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Our Load of Mutations[1]

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1. The "prevailing" view.

While a few students of heredity have maintained that hereditary diseases and certain congenital anomalies and malformations in man not infrequently may arise from mutation, although unable to present any indisputable evidence in proof of their hypothesis, until recently the prevailing view has been that mutation as a direct cause of disease is extremely rare and of little practical significance. Since observational data are limited to relatively few generations and since human cross breeding experiments may not be performed, we shall never be able to demonstrate with certainty that a hereditary human disease arises from mutation.

The above is quoted from an editorial entitled "Mutation as a Cause of Disease," which appeared in the *Journal of the American Medical Association*, on November 8, 1947 (vol. 135, page 644). The article proceeds to list some 18 ailments (most of them very rare ones) which, to use its terminology, "are believed to occur as mutations." In regard to the form of their inheritance, the further word of caution is sounded that "any given hereditary disease may be recessive, dominant or intermediate depending on the length of time that has passed since the disease-inducing gene arose through mutation, the younger ones being recessive and the older ones tending more to be dominant." It is however concluded that "One of the most important tasks of medical genetics in the future will be to investigate further the significance of mutation as a cause of disease."

It is the aim of the present paper to bring forward some of the considerations opposed to the allegedly "prevailing view" cited above. These considerations would lead to the conclusion that mutation as a cause of impairment of human functions (it would be better not to risk semantic confusion by using the ostensibly more technical term "disease" here) is much more general and goes a good deal further than is commonly realized.

Unless we discard our entire "Mendelist-Weismannist-Morganist" conception of the process of evolution, founded on studies of the most diverse organisms, the whole make-up of a man is the result of a tremendous succession of mutations that happened to succeed, but the ones which did not succeed, that

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is, those causing dysfunction, were and are ever so much more numerous in their origination and of far more varied kinds. It is a poor elementary course in genetics which does not bring out the fact that each bodily process and part is the resultant of the activity of multiple genes, every one of which is subject to its varied mutations, some with smaller, others with larger effects. That is, every one of the thousands of genes that resulted from successful mutations is liable to further change, and its next mutation will most probably be a harmful one. Hence there must be a far greater number of different kinds of ailments whose characteristics are traceable to genetic changes of natural origin than there are different kinds of infectious diseases. This general reasoning does not in itself give us much idea, however, of the actual frequencies with which these mutational disorders occur in populations. For this it is necessary to turn to quantitative studies.

2. The basic theorem of mutant gene frequencies, in cases of regular dominants.

As long ago as 1921 the fundamental theorem concerning the frequency, in a large population, of a disorder caused by mutation of a given gene was laid down by C. H. Danforth, in his address to the 2nd International Congress of Eugenics, held in New York City. This theorem may be expressed by saying that the frequency of the disorder among the individuals of the population (i.e. the proportion of individuals that manifest the disorder) reaches an equilibrium value (f) when it is equal to the frequency (n) with which new cases manifesting it are arising by mutation[2] in each generation, multiplied by the persistence (p), that is, the average number of generations during which a mutant gene of the given type manifests itself in the population before becoming eliminated by selection. At this equilibrium frequency the mutation rate equals the elimination rate; that is, the mutant genes in question are being destroyed as fast as they arise and hence remain approximately constant in number.[3]

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[2] Under this method of formulation (involving a slight modification by the present author) a case of a recessive condition must be counted as "half new" and given a value of $\frac{1}{2}$, if the individual manifesting it has received from one parent a mutant gene which is manifesting itself for the first time (and is therefore in this sense "new") and from the other parent a like mutant gene which has manifested itself already in one or more previous generations (and is therefore "old").

[3] It happens that at this same congress (the proceedings of which were not published until 1923) R. A. Fisher announced the first calculations concerned with the extent to which mutant genes would increase and decrease in numbers as a result of accidental processes of multiplication, a phenomenon later termed "drift" by Wright. He also showed the interaction between this phenomenon and selection, and pointed out in what manner Mendelism and mutation theory serve as a basis for Darwinian evolution. And in the same session as Fisher's paper was presented the present writer gave an outline of the now accepted theory of gene mutation and showed that in consequence of the unremitting succession of mutational occurrences, the frequency of mutant genes in general must rise, with resultant degeneration of the biological organization, when selection is withdrawn, either with regard to any given character or to the whole organism, as the case might be.

Stated in this form, which is approximately that used by Danforth, the principle can for dominant autosomal genes be very readily visualized (fig. 1). Let us however deal first with objects more familiar to us and suppose that a certain trucking company buys two new automobile trucks each year. (When we make our transition to the genetic situation the two trucks represent two

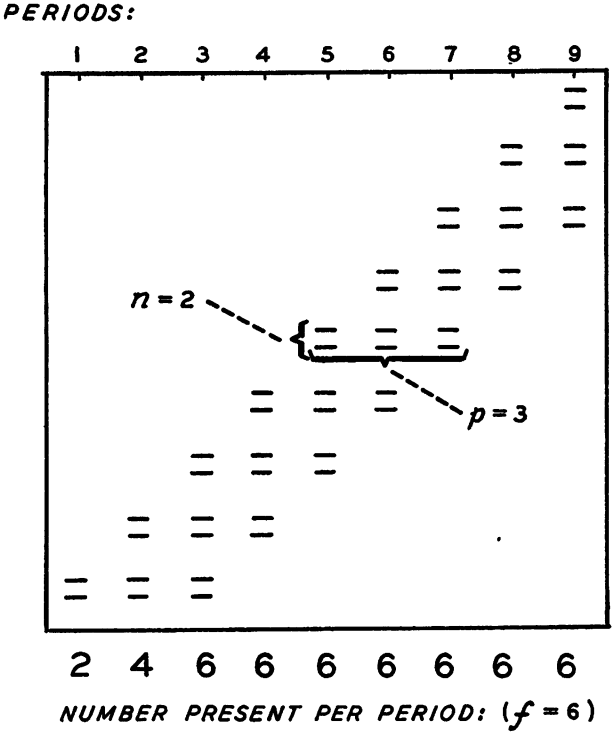

FIG. 1. *How Equilibrium is Attained and Maintained for Autos per Year and for Dominant Mutant Genes per Generation*

Here time proceeds from left to right. One dash indicates the existence of one auto during one year or of one dominant mutant gene during one generation. The persistence of the same auto or gene during later periods is shown by further dashes on the same horizontal row. In this illustration the number of new cases introduced per period, n, is 2, and their number of periods of persistence, p, is 3. The number present in any period is found by adding up the dashes in any vertical column. It is seen that, after a preliminary process of accumulation, this number fails to increase, attaining an equilibrium value, f. In the illustration f is seen to be 6, and it is obvious that $f = np$. That is, the elements accumulate until there are as many present in a vertical column as in any group of rows that began at a given time.

new dominant mutations of a certain kind arising among the individuals of a population in each generation.) In this example, then, n, the new cases, when expressed in numbers, is equal to 2. Suppose next that these trucks always wear out sufficiently at the end of three years to cause them to be gotten rid of. (This corresponds to the dying off of the dominant mutant gene after three generations.) The persistence, we then say, is for three periods, and $p = 3$. As the diagram shows, an equilibrium value (f) of six accumulated trucks (or genes)—adding the dashes in a vertical column—is reached in the third year (or generation). And this value of f, 6, for the accumulation reached, which remains constant thereafter, is equal to the rate of origination per period, 2, multiplied by the number of periods of persistence, 3. That is, $f = np$.

Of course, when we deal with genes instead of trucks the number originating in each period, or generation, and more especially the number of periods of persistence, are subject to fluctuations. They are not themselves ordinary mathematical constants, as they are shown to be in the diagram for the sake of simplicity, but they only have a certain average value. However, when the number accumulated at equilibrium is much greater than 6, lying in the hundreds or thousands, these fluctuations can have relatively little effect on the number arrived at in the long run. To be sure, the attainment of the equilibrium number is greatly delayed by the variations in persistence; in fact, the equilibrium number is, for this reason, only gradually approached, as a limiting value. The speed of approach is calculated according to another formula, which was also first worked out by Danforth, in the same article.

The persistence number, giving the average number of periods during which a gene manifests itself before dying out, is of course the reciprocal of the figure for the amount of selection against the gene on each occasion on which it manifests itself. Thus, in our chosen case, where the average persistence is three generations, the mutant gene, every time it appears, has a one-third greater chance of dying out than a normal gene has. It may, to be sure, happen to die out after only one generation or it may on the contrary manage to survive for many generations—meanwhile even multiplying in some instances. Nevertheless, as various geneticists (among them Jennings, Wright, Wentworth) pointed out in the second decade of this century, these opposite accidents of survival which occur apart from selection must ultimately compensate one another in a large population. It follows that if a large number, n_l, of mutant genes of a given kind were considered, all of which had a one-third greater than normal chance of dying out at any one manifestation, then all of them taken together would go through approximately $3n_l$ manifestations.[4] That is, if i designates the amount of impairment or "selective disadvantage," i.e. the chance (in our case, $\frac{1}{3}$) of dying out at any given manifestation, we have the relation $i = 1/p$,

[4] A proof by summation of the numbers in each generation (sum of factorial series) is sometimes given for this. However, no proof is required because the very definition of the chance of elimination is necessarily the number of eliminations (n_l) divided by the total number of cases (here $3n_l$). It should be noted however that p, the *average* number of manifestations of a given gene (in our case 3), is considerably larger than the *median* number of manifestations, since the distribution is much skewed. It can be reckoned that when p is a large number, only 0.37 of the genes succeed in going through the average number of manifestations. But those which do succeed manage to exceed the average number, on the whole, by a good deal more than those which fail fall short of it.

or $p = 1/i$. On the other hand, the mutant gene's chance of survival, s, in any generation, often called its survival value, is $1 - i$, or in our case $\frac{2}{3}$.

It is evident that the relation $f = np$ may be used to determine n, the frequency of new cases (or that of cases eliminated, since these are ordinarily equal to n), provided f and p are known. However, when it is used to determine the mutation rate per genome or gamete, μ, it must be remembered that the frequency of manifested cases (i.e. of mutant phenotypes) among individuals in a population is, for infrequent dominants, approximately twice the frequency of the mutant gene among the genomes or gametes, since an individual results from a combination of two germ cells and manifests a dominant gene received from either one of them. Therefore the frequency of new cases, phenotypically considered, is for such genes (ignoring the very rare occurrence of homozygosis) twice the mutation rate: that is, $n = 2\mu$. Likewise, the frequency of individuals eliminated genetically by the given gene at equilibrium, being equal to n, is 2μ. Substituting this value of n in the formula for f we have, for infrequent dominants, $f = 2\mu p$, or $\mu = f/2p$. In our preceding illustration, then, $\mu = 1$, when expressed in whole numbers, with the population size, N, understood. Actually this means that there is a *frequency* of mutation of $1/N$, where N may be thought of as the total number of gametes of a given sex that function in producing a population of the size there under consideration.

3. The theorem in other cases.

Strange as it may at first seem, the fundamental formula, $f = np$, applies as well for completely recessive mutant genes as for dominants. However, in this case, when we solve for μ, the factor 2 does not enter; that is, we have simply $n = \mu$. The situation for completely recessive mutant genes has been schematized, again in much simplified form, in figure 2. Each horizontal row in this figure shows the situation for a given mutant gene through a succession of generations. The gene is again represented as being handed down without either multiplying or dying out, until selection intervenes to destroy it, since as has been noted above this will happen as an average of all cases. In this case we have again supposed two new cases to arise per generation ($n = 2$). And, as before, the persistence, p, i.e. the number of manifestations of a gene, has been taken as a constant number (again 3) instead of being, as it actually is, subject to such fluctuations that the frequencies of its values form a geometric series resulting in the given number as the average.

In this figure, unlike that for dominants previously dealt with, we have distinguished between cases of manifestation of the mutant gene and cases of its presence without manifestation. Only the former have been represented by dashes, the latter by dots, and it is only the former that have been counted in the determination of p. That is, a gene's "persistence" here denotes the number of its manifestations (dashes), not its duration or the total number of generations of its survival. This persistence is the reciprocal of the selection which operates against it when it does manifest itself, i.e. in the illustration chosen there must be an adverse selection of $\frac{1}{3}$ per manifestation. And it is the manifested cases, not the total cases carrying the gene, which accumulate to the

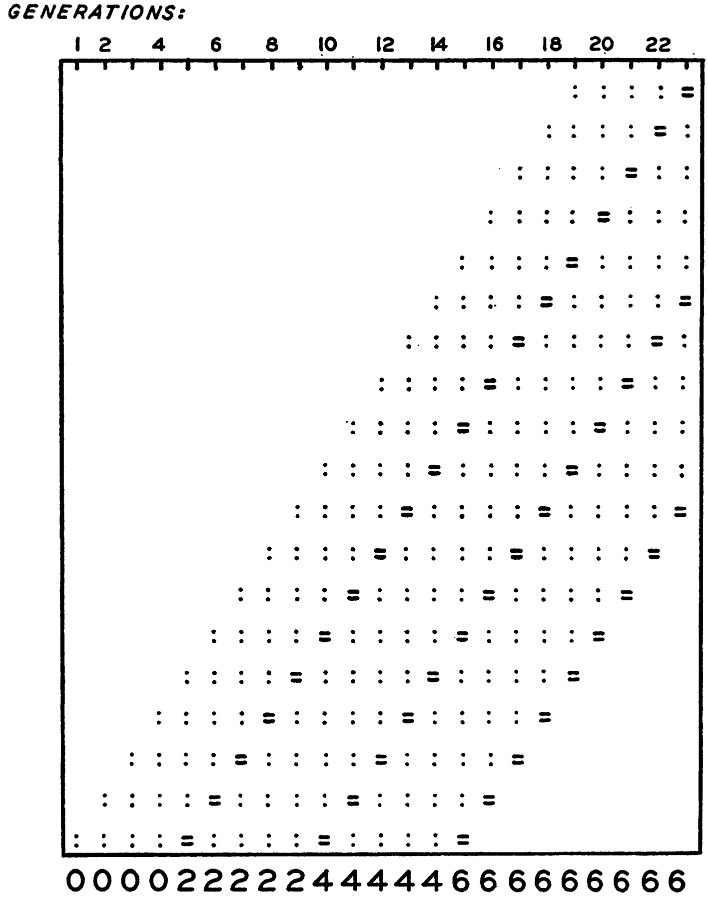

FIG. 2. *Simplified Diagram of the Mechanism of Equilibrium for Completely Recessive Mutant Genes*

The method of symbolization is the same as in figure 1, except that the mutant genes are represented by dots when they are present in heterozygous condition and therefore not manifested and are represented by dashes when homozygous and manifested. As before, n is taken as 2 and p, which is here the number of generations a gene is manifested before dying out, as 3. Again $f = np$, which in this case is 6.

equilibrium frequency calculated by this value of p: for this illustration, an equilibrium frequency of 2×3, as before. However, as above noted, the mutation rate per genome or gamete, μ, is now n instead of $n/2$, and in our illustration this is seen to be 2. That is because each case of manifestation or of elimination now applies simultaneously to two mutant genes, one derived from a gamete of each sex. Of course the same two genes do not keep company as shown, yet the numerical relations here in question average out as if they did.

It is to be noted that, except for recessive genes of extremely high persistence, the manifestations will occur but rarely, since they result from the coincidence of the same recessive gene having been received from both parents. Thus the dashes are usually separated by far more dots than here shown. However the relations would remain in principle the same as shown. We have preferred to abridge our representation in order to conserve space and to make the matter easier to apprehend. The diagram is also simplified in not showing great variations in the numbers of consecutive dots, and in not having these numbers greater before equilibrium and gradually diminishing until it is attained. None of these simplifications affect the final equilibrium value nor the fundamental relation $f = np$.

With dominants of incomplete penetrance the same scheme of representation could be used, i.e. the cases of non-manifestation could be shown by dots and the value of p could be based on the manifested cases only. However, it seems unlikely that there would be many mutant genes which in the apparently non-manifested cases were completely lacking in any influence on survival, and unless this were true the apparently non-manifested cases would have to be taken into the reckoning for i and p. As a matter of fact, the same stricture also applies against the representation of heterozygous recessives by dots, except when the recessivity of the mutant gene is complete. As we shall see later, this makes the formula for complete recessives of interest only as a limiting case.

Completely sex-linked recessives, unless so very frequent as to appear in the female with a frequency comparable to that in the male, can with close approximation be treated in our scheme of pictorial representation as dominants of incomplete penetrance which, regardless of their mutation frequency, show in every third generation on the average. Their diagram, corresponding to figure 2, would show two dots to each dash. This is because one-third of a population's X-chromosomes exist in its males, so that there is, in general, one chance in three of such a gene, at any given time, being in a male zygote. Now since the vast majority of manifestations of these genes is concentrated within the male portion of the population, even though the males contain only one-third of all the X-chromosomes, it follows that the frequency in the males of new cases showing up for the first time (and therefore, too, the frequency of males eliminated by such genes, at equilibrium) must be $3\mu_x$, that is, three times the frequency, μ_x, with which these mutations actually arise in the entire collection of X-chromosomes of the population, for they wait until they do get into a male before they show. But as the males constitute half the population, the equilibrium frequency of new cases and of elimination in the population as a whole must be $3\mu_x/2$ (a value deduced in a less direct way by Haldane, 1937).

To obtain the equilibrium frequency of manifestation among males we must multiply the figure for new or eliminated cases among them, $3\mu_x$, by the persistance value for males, $p_{♂}$ (or, what amounts to the same thing, divide it by the selective disadvantage for males, $i_{♂}$), thus obtaining the expression $f_{♂} = 3\mu_x p_{♂}$. Dividing this by 2, we find that, for the manifestation frequency in the population as a whole, $f = 3\mu_x p_{♂}/2$.

It should be noted that each sex-linked recessive mutation, like each dominant and unlike a complete recessive in an autosome, is in the male a full cause of manifestation. It follows that when it occasions elimination it is also a full cause of zygote death, i.e. the cause of two genome deaths, like a dominant gene. This becomes more evident if in the case of completely sex-linked mutant genes we define μ, for any locus in the X-chromosome, as the frequency of new mutant genes among the entire collection of gametes, whether from male or female, that function to produce the next generation, just as we do in the case of non-sex-linked genes, instead of using the special coefficient μ_x, which we defined as the frequency of mutations among just those gametes that carry an X-chromosome. Since one quarter of the functioning gametes (half the sperm) carry no X and therefore have a mutation rate of 0 for these loci, the value of μ on our more general definition must be $\frac{3}{4}$ of the value, μ_x, which was determined by the more special definition employed above. Making allowance for this in the above formulas by dividing them by $\frac{3}{4}$, we find that, on the more general definition of μ, we have for recessive sex-linked mutant genes n (the frequency of new cases or of individuals eliminated) $= 2\mu$, and $f = 2\mu p$, just as for dominant autosomal genes. It is evident that the same formula would necessarily hold for dominant sex-linked genes also, and for all having intermediate grades of dominance. As in its application to autosomal dominants, this formula would lose accuracy only in cases in which the detrimental action was so very slight as to allow a considerable proportion of individuals to have received the gene from both parents (these would of course be homozygous females, in the case of sex-linked genes).

For the important—in fact, the usual—case of a non-sex-linked gene which is incompletely recessive, manifesting itself to some extent in the heterozygote but more in the homozygote, we have a situation combining the features of the case for autosomal dominants and of that for autosomal complete recessives, but the exact calculation is more complicated. For the persistence now depends on the amount of selection in the heterozygous as well as in the homozygous mutant individuals, and on the ratio of these two types to one another. However, this ratio varies with the gene frequency, and the latter in turn is determined not only by the mutation frequency but also by the persistence itself. Thus, in this case, the values become interrelated in an intricate way. We shall not digress here to take up the resultant formula. Fortunately however it is unnecessary to use this more complicated formula when the heterozygotes so outnumber the homozygotes that, despite the smallness of the selective disadvantage of the heterozygotes, nearly all the elimination of the mutant gene occurs in them. Under these circumstances we may ignore the homozygotes, and incur little error by using the simple relations for dominants, $f = 2\mu p$, and n (or frequency of elimination) $= 2\mu$. As we shall see later, it is probable that the great majority of mutant genes fall into this category.

4. Mutation frequencies of individual human genes, as thereby determined.

The first serious attempt to gain knowledge of the mutation frequency of a human gene was made by Danforth in his address of 1921. Using the principle which he had worked out for dominants, he applied it to the cases of syndactyly and polydactyly in man, both of which were already known to be inherited as dominants. From the records then existing, he was able to estimate the frequencies of each in the population as approximately 1 in 1,000 individuals (i.e. 1 in 2,000 genomes) and also the fact that in both cases their persistence must be at least three generations and probably was more. The formula then showed that their rates of origination by mutation must, in each case, be less than 1 in 6,000 germ cells—though how much less could not be determined without more accurate figures for persistence. As he further stated: "There is a considerable number of dominant traits which are probably slightly unfavorable and which have an incidence not greatly different from that of syndactyly. . . . The frequency could be estimated if the average number of generations through which they persist were known, but it is very doubtful if the maximum frequency [of mutation] is often greater than 1:6,000."

The value thus assigned still stands as an approximate upper limit and Danforth's suspicion that the mutation frequency per locus is usually lower than this is supported by the work done in the past decade and a half by Haldane, Penrose, Mørch, Dahlberg, and others, using in most cases substantially the same method on the more accurate data since obtained for other genes—both dominants and sex-linked recessives. Values of μ most of which range between about 1 in 25,000 and 1 in 75,000, and appearing to center about 1 in 50,000, have been obtained in this way for some half dozen other genes. They have recently been summarized by Haldane (1948–9). Some of them have been corroborated by the more direct method of determining, in sample groups, the number of cases arising as demonstrably new mutants, from parents who did not carry the gene. Dahlberg also, in using a special type of approach to the estimation of persistence (or selection), based on the ascertainment of the number of ancestors manifesting a trait, has (1948–9) obtained results in the above range.

The values of mutation rate arrived at by even the improved techniques are admittedly maximal, when applied to a given locus. For there is no assurance that one is dealing with the results from only one locus, rather than two or more loci the mutations of all of which give the same kind of phenotype. However, the rough agreement in the values for different abnormalities argues in favor of their being of the right order of magnitude. In time, light might be thrown on this matter by studies of linkage of some of the genes in question with common marker genes, such as antigens.

In the case of apparently recessive genes the difficulties appear too great for profitable application of any of the formulas for the estimation of μ. In the first place, there is as we shall see good reason to infer that most of them have a slight degree of dominance, enough to make the formula for complete recessives inapplicable to them. At the same time there is too great uncertainty as to the value of p (or i) for the heterozygotes in these cases to allow a numerical solution on the basis of the formula for dominants. This is particularly true of very weakly acting dominants like these, for their i values for heterozygotes are not only so small as to be indeterminable at present, but have also been subject to especially great and especially indeterminable alterations caused by the changing conditions of civilization. Finally, there is reason to infer that, insofar as these genes are functioning as recessives, their average frequencies of manifestation have been significantly lowered below the equilibrium value in recent generations by the merging of many small populations into larger ones.

5. Method of calculation of total frequencies of elimination and of manifestation.

From Danforth's observation that all detrimental mutant genes, of whatever grade, tend to equilibrium frequencies at which their extinction rate simply equals their rate of origination by mutation, μ, it follows very directly that the grade of detriment occasioned by a gene when it manifests itself in an individual has no influence upon the amount of genetic death it causes in the equilibrium population. For its death rate depends only on its mutation rate.[5] And since the death rate is a kind of index of the total damage which the gene occasions, it also follows that, paradoxically, the grade of detriment caused by a gene in the average individual in which it manifests itself is not correlated with the total amount of damage it does in the entire population. All this results from the fact that a less detrimental impairment accumulates to a compensatingly higher equilibrium frequency than a more detrimental one of the same mutation rate, i.e. that $i = 1/p$. In the entire population, then, just as

[5] The above relation was made use of by Haldane in 1937 (*op. cit.*) in his pioneer calculations on the total "loss of fitness" caused in a population by mutation. More recently, without at the time being aware of Haldane's approach to this particular point, the present writer gave a statement of it in terms of the individual mutation, noting that each detrimental mutant gene, no matter how slight its phenotypic effect, produces, on the average, one eventual half-death of a zygote, or what may be termed one genome-death, when it acts as a recessive in causing elimination, and one complete zygote death, i.e. two genome deaths, when acting as a dominant (Muller, 1947, 1948, as well as lectures and unpublished communications of earlier dates).

many individuals are being exterminated by the less detrimental gene, and it is on the whole doing as much collective damage in others, not exterminated by it, as would have been the case if it had been more detrimental in its effect on single individuals and had therefore accumulated to a lesser degree.

It is a direct consequence of the above facts that the elimination rate of all mutant genes taken together must at equilibrium be equal to μ_t (or $\Sigma\mu$), that is, the sum total of the respective values of μ for all loci, without consideration of detriment, i, or persistence, p. This total value may also be expressed as $l\bar{\mu}$, where l is the total number of loci and $\bar{\mu}$ is the average per-locus mutation rate.

When however we come to figure the total amount of genetically caused elimination of *individuals* rather than of genes the situation becomes somewhat more complicated, first by reason of dominance and second by the fact that genes at different loci will have some overlapping of their extinction effects, i.e. their incidence will to some extent be on identical individuals and therefore not separately to be recorded. Considering first the effect of dominance, we have already examined the formulae applying to individual loci. According to these, the equilibrium relation for dominant autosomal genes, as well as for sex-linked (dominant or recessive) genes, is that n, the frequency of new cases, i.e. of individuals with newly manifested genes, and therefore too the frequency of eliminated individuals, is 2μ, while for nearly completely or completely recessive autosomal genes it is $<2\mu$, with a lower limiting value equal to μ itself. All these cases may be represented as $d\mu$, where d denotes the factor which, depending on the degree of dominance, varies from 2 down to 1.

Considering next the question of "overlapping" referred to above, it is evident that in a large panmictic population there would be very little correlation between the distributions of the mutant genes of different loci and that these distributions may for the present purposes be considered independent. Moreover since, firstly, the extinction rate due to an individual locus is exceedingly small and since, secondly, in the great majority of cases the extinctions caused by any given locus are probably only in small proportion (relatively to the whole) determinately connected with those caused by particular genes at other loci, we may tentatively and as a first approximation consider the genetic deaths associated with different loci as occurring independently. If now the sum of the respective $d\mu$ values for the individual loci is itself not above 10%, the amount of "overlapping" of the genetic deaths caused by mere coincidence will be relatively small. Therefore this sum, $\Sigma(d\mu)$, having a value lying between $l\bar{\mu}$ and $2l\bar{\mu}$, will in that case give a fair approximation to the frequency of genetic deaths of individuals.[6] Calculations of this kind have been made in

[6] As in other cases where the total frequency of a phenomenon caused by any one of many independent events is to be calculated (as for instance in plotting points on the curve relating mutation frequency to X-ray dosage—see Muller, 1936), strict accuracy always requires us to multiply to-

some detail by Haldane (1937) but, like others who have previously dealt with the subject (including the present author), he has treated autosomal mutations in general as complete recessives and hence has taken μ as the frequency of elimination of individuals caused by a given locus, thus arriving at a total elimination rate of individuals which approximated μ_t (or $l\bar{\mu}$).

We may turn next to the method of calculating, not the total frequency of elimination of mutant genes or of individuals, but their total frequency of manifestation. This is a much larger quantity since the persistence, p, now comes into the reckoning. For each locus considered by itself we saw that the manifestation frequency at equilibrium is μp, multiplied by a coefficient which varies from 2, for effectively dominant mutants, down to 1, for complete recessives.[7] If now the values of μ and p for all loci are uncorrelated and the coefficient is for the great majority of loci substantially 2, then the total manifestation frequency becomes $2\ l\bar{\mu}\bar{p}$, where $\bar{\mu}$ and $\bar{p}$ are the arithmetical means of μ and p, while if the coefficient were significantly below 2 and also uncorrelated with μ and p its average could be substituted for 2 in this expression.

It is, however, very probable that there is some (but not a very effective) degree of positive correlation between all three factors, μ, p and the coefficient that depends on dominance. For loci giving mutants of higher p, i.e. of lesser grades of impairment, would be less efficiently selected for high genetic stability, and would therefore tend to have higher values of μ. They would likewise be less efficiently selected for high phenotypic stability, and their normal alleles would therefore tend to be less dominant over the hypomorphic mutants, i.e. the latter would have a higher dominance relative to the normal than where persistence was lower.[8] The resulting association of higher p, higher μ and higher coefficient would cause the sum of these products to be higher than if the factors varied independently. There would therefore be a larger total number of manifestations, although the manifestations, considered separately, would on the average be of lesser degree. Thus, any value for total manifesta-

gether all the chances of *non-occurrence* (in our present case, the chances of survival, $1-\mu$ or $1-2\mu$, as the case may be). This gives the combined chance of non-occurrence (here, of survival). This combined chance is then subtracted from 1, for obtaining the total chance of occurrence (here, of extinction). However, when this total chance of occurrence (extinction) is itself below 10% this procedure is usually unnecessarily refined. For in that case the amount of overlapping of the individual occurrences (extinctions) is so small that the total occurrence (extinction) can be calculated, with an error of less than 5% of its own value, by the simpler method of simply adding together the individual chances of occurrence.

[7] This coefficient is not identical with the d used in the formula for elimination frequency but somewhat larger, because it depends upon the relative numbers of heterozygous versus homozygous manifestants that *occur* rather than upon those that are eliminated. Thus wherever d may be taken as 2 the present coefficient may with even closer approximation be so represented.

[8] As was pointed out by the present writer (1918, p. 494) "it is to the advantage of the organism that most genes shall be very stable, and present-day races are doubtless the products of a long process of selection in that respect as well as in regard to the constancy of the reactions whereby the factors produce the characters."

tion frequency calculated by one of the formulae given above, which assume independence of the factors, would be a minimal value.

Regardless of such niceties of calculation, the total frequency of manifestations of mutant genes is, as we shall see, certainly far above the 10% limit which we set on page 121, above which the method of summation should not be applied for determining the frequency of affected *individuals*. That is, the sum of the manifestation frequencies for all loci, although it does serve to represent the total frequency of manifestations of mutant genes, quite fails to represent, even to a first approximation, the frequency of the individuals that have these manifestations. For the manifestations are so abundant that their incidence for different genes overlaps to a very considerable degree, leaving practically no individual free from one or more manifestations. Thus the value arrived at by summation rises considerably above 1. Nevertheless this value still retains its usefulness, since, although it no longer represents the frequency of individuals with manifestations, it does represent the average number of manifestations per individual of the population.

6. The distribution and total frequency of mutations, as evidenced in Drosophila.

All these inferences and formulae remain dry as dust until applied to the actual situation. What evidence is there concerning the total frequency of mutation, the relative frequencies of mutations with different grades of detriment, the amount to which they act as dominants or recessives, and, finally, the degree and manner in which the population is encumbered by them? For this let us turn first to pilot experiments on *Drosophila*.

In *Drosophila* work, recessive lethals have long been used as an index of mutation rate since they comprise a class which is much more sharply and objectively defined, as well as more abundant, than that of visible mutations. Moreover, evidence has been obtained that most of them, especially when "spontaneous," are gene mutations, not differentiated from other gene mutations in the basic processes by which they arise. If now we exclude demonstrable structural changes of chromosomes, we find sensibly the same ratio of lethal to visible gene mutations in the spontaneous as in the X-rayed material. It therefore seems legitimate to infer that the gene mutations induced by X-rays in *Drosophila* have on the whole (although not necessarily locus by locus or allele by allele) the same relative frequencies of the broader phenotypic categories as do the spontaneous ones. This allows us to turn to the X-rayed material for a survey of these relative frequencies, inasmuch as data on this matter in spontaneous material are as yet inadequate.

It was one of the first observations of the present writer in the mutation work that, considering any given morphological character, mutations with smaller effects exceed in their frequency of occurrence those with larger effects (Muller, 1923; Altenburg & Muller, 1920, p. 47). This was not contradicted by the finding that the frequency of lethals exceeds that of visibles by some 5 to 10 times, for it seemed probable at the same time that "invisible" mutations affecting viability detrimentally yet not enough to be fully lethal were more abundant than those drastic enough to be classed as lethals. In the first X-ray work on mutations, the results of casual observation did seem to bear out this idea (see Muller, 1928*a*), but there were no quantitative data on the matter until 1934. In that year, by coincidence, Kerkis and the present writer in collaboration (Muller, 1934; Kerkis, 1935, 1938) and Timoféeff-Ressovsky (1934, 1935), using similar techniques, carried out quantitative tests of the frequency of lethal and of invisible detrimental mutations of varying grades, induced by X-rays in the X-chromosomes of *Drosophila* spermatozoa. The results agreed surprisingly well. They showed the "detrimentals" to be induced with two or three times the frequency of the complete lethals, and, in the most delicate experiments of Kerkis, which were capable of detecting detrimentals of somewhat slighter grade, the detrimentals arose with as much as four times the frequency of the lethals.

We can now take into account the fact that about a third of the lethals induced by X-rays in *Drosophila* spermatozoa at the doses used involve deficiencies or other structural chromosomal changes, whereas only some 5% of the non-lethals do so. When we make allowance for this we find that the detrimental gene mutations must exceed the lethal ones by something like five times; in other words, lethals and detrimentals together would have six times the frequency of lethals alone. But even this does not bring into the reckoning mutations with grades of detriment, as recessives, of less than about 10%, i.e. with 90% or more survival value, for the tests were not delicate enough to detect them. It is quite conceivable that these slightly detrimental mutations may have an abundance comparable with that of all the more markedly detrimental mutations taken together.

Let us now see what these findings mean in terms of the total spontaneous mutation frequency, μ_t, and of the total detrimental effect in populations. Experiments of my own and of my collaborators, as well as of others, have shown that the frequency of origination of lethals in the X-chromosome of *Drosophila* is only about one-sixth their frequency in all chromosomes taken together—a result in approximate agreement with the relative sizes of the euchromatic regions of the different chromosomes. This would make the total frequency of lethals and recognized detrimentals (not counting those of too slight effect to have been detected), in gametes containing an X-chromosome, some 36 times as great as that of lethals in the X-chromosome. In the gametes not containing an X (spermatozoa with a Y) this "total" frequency would be five-sixths as great as in the rest, and since three-fourths of all functioning gametes have an X, this gives us for the total gene mutation rate in all functioning gametes taken together the value $(36 \times \frac{3}{4}) + (36 \times \frac{5}{6} \times \frac{1}{4})$, i.e. 34.5 times the frequency of just the lethal gene mutations in the X-chromosome alone.

Now the frequency of *spontaneous* lethal gene mutations in the X-chromosome of male *Drosophila* is usually about 2 per thousand in sperm of the first week after hatching and only about 0.6 per thousand thereafter (Muller, 1946, and unpublished data). We may call this, to be on the conservative side, an average of 1.3 per thousand, although probably so many flies die in nature after the first week as to make the average higher. In the X-chromosome of the female the frequency is about 1.7 per thousand throughout life (Muller, *op. cit.*). Ignoring for present purposes the fact that the female furnishes more X-chromosomes than the male (since that is not true of the other chromosomes) we obtain an over-all figure of 1.5 lethals per thousand in the X-chromosome, a figure which is if anything too low. This may now be multiplied by 34.5 to obtain the frequency of all lethal and detectable detrimental gene mutations in all the chromosomes together. The resulting value turns out to be 51.75 per thousand, or approximately 5%.

A "total" mutation frequency of 5% means that 1 gamete in every 20 contains a new spontaneously arisen lethal or detectable detrimental gene that arose within the span of the very last (the parental) generation. But, as we have seen, each detrimental mutation, no matter how slight its effect, as well as each lethal, eventually leads to one genetic death of a zygote or genome, on the average, and these mutations are arising in the germ cells of both parents. Therefore, insofar as the deaths occur in homozygous recessives, 1 in 20 of the population at equilibrium would be genetically eliminated while, insofar as the deaths occur in heterozygotes, through some dominance of the mutations, or in hemizygotes, through the action of sex-linked genes in males, twice this number, or 1 in 10, must suffer genetic death. (This is of course on the assumption that the genetic causes of death act, in preponderant measure, independently of one another.)

Before attempting to draw further conclusions from the figure $\mu_t = 5\%$ which we have just arrived at, it may be well to check it by a second method, even though this is subject to greater error than the one used above. This second method makes use of the relation $\mu_t = l\bar{\mu}$. The most reliable estimates thus far made of l, the total number of loci, in terms of the number of genes of a complete X-chromosome-containing *Drosophila* gamete (Muller, 1935*b*), agree on a minimum of 5,000 to 10,000 genes. (This would make 4,800 to 9,600 as the average for all functioning gametes, including both those which do and those which do not contain an X; the correction for the sex chromosomes is so much less than the range of error it is not worth our while to make it here.) Now the average spontaneous mutation rate per individual locus, $\bar{\mu}$, has hitherto been a matter of considerable uncertainty. However, during the past two years it has been found in our laboratory, in work participated in by the present writer, J. I. Valencia, and R. M. Valencia (1949), that for a sample of 9 loci giving visible mutations the usual frequency of changes affecting the characters in question is probably 1 in about 100,000 gametes, with the great majority of the loci falling into a comparatively narrow range about this value. If now we take this as the average and multiply 1 in 100,000, the $\bar{\mu}$ per locus, by the number of genes, l, taking this only as the lower minimum, 5,000, we obtain a frequency of 1 gene mutation in some locus or other among 20 gametes. Although this result is practically identical with that obtained by our previous method the two calculations were quite independently made and the closeness of fit found was entirely unexpected.

The above remarkable agreement must of course be accidental to some extent. There may in fact have been twice as many genes as the 5,000 assumed on our second method, and, if so, we should have obtained a value for μ_t of 1 in 10 instead of 1 in 20. Such a value, however, would be readily reconcilable with the 1 in 20 found by the first method, by making the assumption that, in the experiments on the frequency of detrimentals, there had been as many mutations of too slight a grade of detriment to have been detected as of those whose existence had been demonstrated. At any rate, we may feel, through the check provided by the second method, fairly confident of our figure of 1 in 20 as representing a *minimum* value.[9] This shows us that, in *Drosophila* at any rate, the spontaneous occurrence of mutation *in some gene or other* is not at all a rare event.

7. On the total frequency of mutation in man.

To what extent may we conclude that in man also mutation is a not uncommon occurrence? Man is so remote from *Drosophila* that we may not, without cogent supporting evidence, carry over any quantitative genetic conclusions from the one organism to the other.[10] Moreover, it is obvious that no mammal at the present time presents data which could be used for a calculation of total mutation frequency by means of the first of the two methods outlined above. Fortunately, however, there are already some results, previously referred to, which can be used in connection with the second method.

As was mentioned on page 119, the values for mutation frequency so far obtained for individual loci in man are in the neighborhood of 1 in 50,000 per generation, or about twice as high as what appears usual for *Drosophila*. Although there may have been more likelihood of studying those genes in man

[9] The same figure was arrived at by Haldane (1937, *op. cit.*) using the first method of calculation and basing it on *Drosophila* data known to him at that time; some of the data used involved rather large deviations, but it happens that these were such as virtually to cancel one another.

[10] It was pointed out by the present writer and Altenburg (1919) that the human mutation rate, expressed as a *time rate*, must be far lower than that found by them in *Drosophila*.

in which mutations occurred oftener, still it would seem strange if the per-locus mutation frequency in man were not higher than in *Drosophila.* In this connection the fact may come to mind that a human generation lasts about 700 times as long as a *Drosophila* generation and therefore affords far more time for the accumulation of mutations. This consideration, to be sure, loses much of its force in view of the evidence (Muller, 1946, and unpublished data) that the occurrence of most mutations, even in *Drosophila,* is concentrated into one or more very restricted periods in the germ cycle. But, despite this stricture, the fact remains that the human germ cell lineage includes two or more times as many cell divisions as that of *Drosophila,* and this is a feature which is probably much more closely connected with mutation frequency than is mere time. So also is the temperature which, averaging considerably higher in the human than in the fly, should tend to give the human a higher mutation frequency.

We should expect these influences to be counteracted to some extent by a correspondingly greater pressure of selection in man as compared with the fly, for such genes as would tend to lower the mutation rate. But it is very unlikely that such genetic compensation would be complete. One reason for this is that there is probably a lesser *efficiency* of selection in man against mutant genes that raise the mutation rate (or, conversely, in favor of those that lower it). This lesser efficiency would be caused, first, by the much greater uniformity in the rate of reproduction of different individuals in human than in fly populations, connected with the production of far fewer eggs by the human. A more uniform rate of reproduction will result in a weaker correlation between the possession, by descendants, of any gene that had increased the mutation rate, and the manifestation, by these same descendants, of the harmful mutational effects of this gene; thus selection against such a gene would be weakened. A further factor making for the decreased efficiency of such selection is the smaller size of the X-chromosome (and especially of its differential region), relative to the other chromosomes, in man than in *Drosophila* (cf. Muller, 1942).

It would also be strange if man did not have more genes than *Drosophila,* or at least a greater sum total of gene parts that could separately get out of order (by mutations of seemingly non-allelic nature), in view of man's undoubtedly greater complexity of both gross and, more especially, histological structure. The larger total bulk of the germinal chromatin of all mammals, as seen even in sperm, which are surely selected for smallness and compactness, and the correspondingly greater frequency with which chromosome breaks are induced by radiation in mammalian sperm as compared with those of *Drosophila,* are much less secure arguments, yet they point in the same direction. All in all, then, we are probably erring very much on the side of "caution" if we assume that the human gamete contains only 5,000 genes (or gene parts) capable of separate (non-allelically expressed) mutations.

If now we take the figure of 1 in 50,000 as representing $\bar{\mu}$, the average mutation frequency per locus, and only 5,000 as l, the number of loci, we find a total mutation frequency, $l\bar{\mu}$ or μ_t, of 1 in 10 gametes in man. Although this result, $\mu_t = 0.1$, admittedly represents a low minimum estimate, yet it is double the minimum estimate which we obtained for *Drosophila*, and it is probably a good deal higher than has commonly been imagined.

Taking 0.1 as the lowest value of μ_t which is at all likely, it is also of interest to obtain some idea of how much higher the actual value might be. We might for instance have taken 10,000 instead of 5,000 as the number of loci in *Drosophila*, and then supposed that man had, in effect, twice as many loci as *Drosophila* has. With $\bar{\mu}$ for man at 1 in 50,000 this would give a value of $\frac{20{,}000}{50{,}000}$ or 0.4, for μ_t. We shall see later (p. 138) that there are other reasons for concluding that the mutation rate in man cannot be much higher than this.

8. The effective dominance of "recessives" in Drosophila.

We have seen that the rate of genetic elimination of individuals in a population is a function not only of μ_t but also of a factor d, which depends upon the degree of dominance of mutant genes and varies between the limits 2 (for the more dominant) and 1 (for complete recessives). We may now inquire into the probable value of this factor, considering first the evidence from *Drosophila*.

At first sight, the answer to our present problem seems easy, since it has been known for over thirty years (cf. Muller, 1918, pp. 466–7; and 1923) that in *Drosophila*, and probably in organisms in general, the great majority of mutant genes are recessive, in the sense of having much less dominance than the normal genes from which they arise. However, as has been pointed out by various persons (e.g. Muller, 1940, p. 252; Dobzhansky & Wright, 1941; Berg, 1942), this knowledge is not precise enough. For a little consideration shows that even a very slight degree of dominance of the mutants will be of preponderant importance, by leading to the elimination of the genes in heterozygotes before they have a chance to become homozygous. And a number of reasons were already given in the *Mechanism of Mendelian Heredity* in 1915, indicating that the recessivity of the so-called recessives is not really complete.

Since the early studies of several mutants of *Drosophila* (vestigial, miniature, white eye, black body, etc.) giving this result, a significant series of facts pointing clearly in the same direction has emerged. One is the finding that in *Drosophila* the heterozygous deficiency of even a comparatively short section of a chromosome, probably containing only some tens of genes, is somewhat detrimental, while that of a somewhat longer section is quite lethal. Moreover, even duplications of chromosome sections have effects of this sort, although, as expected, in somewhat lesser degree.

Another clear line of evidence in the same direction lies in the phenomenon called "dosage compensation." This refers to the fact that most sex-linked genes tested have been found to be provided with a series of modifying genes, called compensators, located elsewhere in the X-chromosome. For, when we study mutant alleles of these sex-linked genes, it is found that the naturally existing sex difference in dosage of these other parts of the X-chromosome renders the effectiveness of the single dose of the given mutant gene which the male has almost exactly as great as that of the two doses which the female has. Nevertheless, it is usually impossible to detect, by superficial observation, any difference between the effects of 1 and 2 doses of the normal allele, even when the compensators are held constant. That is, outwardly, the "dominance" of the normal gene over its absence or over its recessive mutant allele appears complete. Yet, despite this, the effect of a single dose of the normal gene, uncompensated, must be sufficiently different from that of the homozygous normal to have influenced the organism's survival adversely to a significant degree, for otherwise the system of compensators would not have been evolved. Now since the individual heterozygous for a hypomorphic mutant is often much like one having but one dose of the normal gene, uncompensated, we must conclude that the dominance of the normal gene, though sufficient to give a superficially normal phenotype, is often incomplete enough to be effective in lowering the expectation of life or reproduction of the heterozygote. A more extended treatment of this matter (Muller, 1950*a*) has brought forward various further facts in support of this interpretation.

Finally, direct tests of the possible dominance of lethal or nearly lethal mutants have been made or published during the past two years, which clinch the matter for *Drosophila*. There are two sets of data. In the first place, Stern and Novitski (1948) showed that a series of 33 sex-linked lethals, most of them (26) produced by X-raying *Drosophila* spermatozoa, caused when heterozygous an undoubtedly significant lowering of viability. One may reckon from their data that the average disadvantage of the heterozygote in their material is some 10% (a result which would imply, for lethals, a 10% grade of dominance).

Independently of the above work, and before it was published, the present writer, in collaboration with Mr. S. L. Campbell, had started some very similar work, utilizing however autosomal lethals and near-lethals that had been induced in our laboratory by Meyer and Edmondson (see Meyer, Edmondson, L. Altenburg & Muller, 1949) by means of ultraviolet acting upon primordial germ cells in an interphase (polar cap) stage.[11] Thirteen lethals and sublethals were studied, as well as 13 cases of untreated non-lethal chromosomes, to serve as controls. Lethals induced by X-rays in spermatozoa were purposely avoided because of the fact that some 30% of these are deficiencies, involving the more

[11] The work referred to in the above paragraph and that following it was supported by a grant from the U. S. Public Health Service, Division of Research Grants and Fellowships, given on recommendation of the National Cancer Council.

or less cumulative action of an indeterminate number of genes. The ultraviolet lethals, on the other hand, particularly when induced in the extended chromosomes of interphase, would in great majority be one-locus gene mutations, like spontaneous ones. Moreover, tests of some not quite lethal genes also were desired, since in the case of complete lethals one can never know just how drastic the homozygous effect really is and so one cannot adequately assess the significance of a certain degree of heterozygous effect in its relation to the homozygous effect. Finally, autosomal mutants were preferred to sex-linked ones because of the fact that the degree of detriment shown by females heterozygous for sex-linked genes would depend very largely upon the exactitude of the dosage compensation which the given loci had attained and upon related selective factors, difficult to assess, whereas this complication does not exist with the autosomal mutants. The genetic methods used were also very different from those of Stern and Novitski.

Our results, obtained in 1948–49 but only now ready for publication, show a distinct departure from complete recessiveness on the part of both the complete and the partial lethals. In our experiments the grade of dominance of both these classes of mutants averages about 4.5%. However, it is only safe to say that the dominance probably lies between 3 and 6% and *very* probably between 2 and 7%. Stupendous counts would be needed to attain greater exactitude than this.

We have calculated that the difference in average dominance values between the two sets of experiments (Stern and Novitski's and our own) is statistically significant and is of the magnitude to be expected in view of the probable difference in frequency of deficiencies. However, it can also be shown that Stern and Novitski's practice of not including, in their total count of heterozygous lethals versus homozygous normals, individuals which when tested gave cultures below a certain size, was another factor that may have lowered the apparent frequency of the heterozygotes and thus raised the apparent degree of dominance appreciably. For the lethal-bearing individuals (the heterozygotes) must have given smaller average counts in the given type of test and must therefore have been excluded in greater abundance. To what extent lethals in the X may be taken as representative in regard to dominance is, as above remarked, another very problematical question. In view of all these considerations then, as well as considerations of the sizes of the purely statistical errors in the two series of observations, we feel that the earlier data, although based on more genes, should not be regarded as throwing doubt on the quantitative aspects of our own conclusions. That is, it may be regarded as very unlikely that the average degree of dominance of autosomal lethal and near-lethal gene mutations in *Drosophila* lies outside the range 2 to 7%.

Let us next assess what this degree of dominance would mean in terms of our factor *d*, used in determining the equilibrium rate of elimination of individuals from the population. It can very readily be made clear by means of approximation methods that, in a population breeding with the degree of randomness of a human one, an apparently recessive lethal with a dominance of only 2%, even if it had a mutation frequency as high as 1 in 50,000, would produce most of its genetically killing and damaging action on heterozygotes. For the selective disadvantage of 2% in the heterozygote, or 1 in 50, would on the average allow the gene to pass down only through 50 generations of heterozygous individuals, supposing that it remained heterozygous all that time, as it usually would. Moreover, the very rare occasions when it did become homozygous would cause its average persistence, p, to be somewhat less even than 50. Thus the equilibrium frequency of the gene in the germ cells of the population would be somewhat less than 50 times its mutation rate, and, if we take its μ as being 1 in 50,000, its equilibrium frequency would be somewhat below 1 in 1,000. With purely random breeding a given mutant gene of this type would therefore have a chance, in any one generation, of somewhat less than 1 in 1,000 of meeting another gene like itself in fertilization and so becoming eliminated in a homozygote. This chance is so much lower than the chance of 1 in 50, for it to become eliminated in any generation in which it is heterozygous, that it is evident that even the 2% degree of dominance here assumed leads to an amount of elimination and damage of heterozygotes far outweighing that of homozygotes.

We have in the above ignored the effect of inbreeding. In man there would usually be another chance, approaching 1 in 1,000 fertilizations in urban districts or 1 in some hundreds in small, long-isolated rural or primitive communities, for a mutant gene of the given kind to become homozygous through inbreeding of a near or remote nature. Yet, since the chance of elimination in any heterozygote would always remain 1 in 50 for such a gene, we may nevertheless conclude that its chief action in causing elimination of individuals must be exerted through the slight manifestation which it attains in heterozygotes.

The mutant gene of 2% dominance would also wreak much the greater part of its damage short of death in heterozygotes, because the number of deaths serves as a kind of index to the total damage or risk. The individual heterozygote would, to be sure, be far less affected, on the whole, than the individual homozygote, but there would be so many more of the heterozygotes as to much more than compensate, in the production of the total damage, for their individually lesser degree of impairment.

9. Dominance in man.

There are a number of considerations and lines of evidence leading towards the conclusion that the degree of dominance of mutant genes in man is, on the whole, at least as high as in *Drosophila*. These may now be examined.

In the first place, there are good grounds for inferring that the dominance of mutant genes has arisen through a selective process. Whether this selection has mainly occurred, as inferred by Fisher (1928*a*, *b*, 1930), by virtue of the advantage that the dominance of the normal gene confers on the heterozygotes themselves or, as both the present writer (1932, 1935, 1950*a*, *c*) and Plunkett (1932, 1933) later argued, by reason of its stabilization of the phenotype of the homozygous normal in the presence of disturbing environmental and genetic influences in general, the process must be one which only approaches but does not actually attain completion. Thus it would leave a certain degree of dominance to the mutant gene. The incompleteness of the process must be caused, among other things, by the physico-chemical improbability of reaching an absolute maximum of gene effectiveness, and by biological impairments entailed by interference with other processes as such a maximum is approached. It must be caused, further, by mutation pressure tending towards lower levels of gene effectiveness. Another factor must be the occurrence of evolutionary changes in the optimum. And finally, the attainment of perfect precision of dominance would be obstructed by the particulateness or what might be called the "graininess," the ultimately quantized nature, of the processes of mutation, selection and evolution in general.

Now there is no evident reason why the effectiveness of any of the above factors should be less in man or mammals than in *Drosophila*. In fact, as Levit (1936) has pointed out, the far greater ability of the higher forms, and more especially man, to adapt themselves by behavioral means to new and unfavorable conditions, and thus better to compensate for ailments even when they are of genetic origin, should tend, on any selectionist conception of dominance, to make the dominance of normals less complete in man than in *Drosophila*. We may add to this argument that the factors of mutation pressure, recency of change in optima, and graininess, should all be more potent in man than in *Drosophila*, in view (1) of man's higher mutation rate, (2) his greater amount of evolution and consequent destabilization in recent times, and (3) the relatively small number of human individuals that exist either in space (due to their size) or in time (due to their length of generation).

Evidence was presented by Levit in 1934 to 1936, in several memorable papers summarizing the results of a series of investigations by himself and his co-workers, and critically surveying the literature, that recessive abnormalities in man are much rarer, in comparison with dominant ones, than had till then been believed. In these papers, which appeared on the eve of the abolition of his institute and his own "liquidation," he showed that a series of eight different hereditary diseases studied intensively by his group, some of which, such as a prevalent form of diabetes mellitus, had previously been taken for recessives, were all of them in reality dominants. What had been deceptive about them was that they appeared to skip generations but this was shown to be because of their "incomplete penetrance" (usually below 20%). It would be better to say that they commonly remained at such a low level of expression that they could not readily be detected, for in some cases they could be revealed by more refined means (e.g. by blood sugar determinations in the case of diabetes mellitus).

However, as Levit further pointed out, these dominants should only be called "conditional dominants." For the rare homozygous mutant, when known, might be much more extreme than the heterozygous one, as had been proved for a number of genes. In fact, if they had occurred in *Drosophila*, many of these cases would not have been noticed as being abnormal at all when heterozygous, and yet, by reason of the inbreeding so often used in laboratory work with this organism, they would have been picked up in the extreme form, as homozygotes, and hence would have been called recessive visible mutations or recessive lethals, as the case might be. Thus there is no reason to believe that these conditional dominants in man usually depart from the principle that the normal gene has the greater dominance, but they do indicate that despite this the mutant often has a significant amount of dominance.

The evidence that the above relations hold for most mutant genes in man was greatly strengthened by Levit's systematic analysis of the literature on inherited diseases of the skin, eye and nervous system. He showed that of 55 different cases as many as 41, that is, approximately three-quarters, had some demonstrable degree of dominance, and that the great majority of obviously affected individuals in these 41 cases were heterozygotes. The evidence for dominant inheritance was derived from studies (1) of the frequency with which the affected individuals were the products of inbreeding and (2) of the relative frequencies with which different types of relatives of the affected individuals were themselves affected.

Proceeding to a study of the literature on sex-linked mutant genes, which had been considered to furnish particularly good evidence of the prevalence of complete recessiveness, Levit was able to show that in only a very small proportion of cases had this conclusion been well founded. In 24 of the 36 cases reviewed the evidence was found to be insufficient even to classify these genes as sex-linked rather than, for instance, sex-influenced autosomal dominants, while among the 12 cases which could be safely accepted as sex-linked, there were 3 for which the evidence was insufficient to allow conclusions concerning dominance to be drawn. In the residuum of 9 cases, only 2 turned out to be recessive (as judged by the tests then in use), the other 7 all having some detectable degree of expression in the heterozygous female.

Despite the above momentous findings, which have received insufficient attention, there are, all told, not a few apparently recessive abnormalities now established in man, i.e. abnormalities caused by homozygosity of a gene whose effect in the heterozygote has so far failed of detection. Moreover, the ratio of such "recessives" to the "dominants" found would undoubtedly have been a good deal higher, and more nearly like that observed in *Drosophila*, if the circumstances of finding them had, as in *Drosophila*, involved more inbreeding, and less detailed phenotypic observation. Yet, even conceding this, the very fact that these circumstances of breeding and of observation have resulted in a much lower apparent ratio of recessives to dominants in man appears to lead to the conclusion that the apparent recessives in man, if not actually less frequent than in *Drosophila*, have, on the whole, enough dominance to affect their chances of survival significantly in the heterozygous condition (and/or to produce an observable effect on the phenotype of the heterozygous individual). For a permanently low degree of inbreeding cannot result in a lower equilibrium frequency of appearance of homozygous "recessives" in any population unless the frequency of these "recessive" genes has been kept at a low level by means of a selection that was effective against them even when they were heterozygous. This would imply that they were "effectively dominant," in the sense previously explained.

The above argument must be qualified by the consideration (Haldane, 1939*b*) that in recent generations the amount of inbreeding in man has been reduced to a level even lower than in earlier times. This change in the system of breeding (not the low degree of inbreeding in itself) must reduce the frequency of homozygous recessives in the present population below the equilibrium value. However, this influence turns out, on calculation, to be far from sufficient, by itself, to explain the shortage of recessives found in man as compared with *Drosophila*. This is the more true in consideration of the circumstance that some of the best studied groups in man in which dominants have been found have been long settled peasant populations. Moreover, the studies of Bell (1940) on the consanguinity of parents of hospitalized patients did not yield as much evidence of the importance of this factor in morbidity as was to be expected on the view that homozygosity plays a major role in the causation of genetic damage. Similarly, the studies of Bedichek and Haldane (1938), so far as they went, gave no ground for assuming that recessive lethals occur as frequently as might be expected if their origination by mutation were only as high, per generation, as in *Drosophila*, and if they were eliminated only as homozygous recessives.

In further evidence of the conclusions that the great majority of mutant genes in man have a significant degree of dominance, attention should be drawn to the important series of facts brought together by Neel in his address to the American Society of Human Genetics in September, 1948 and published in the first number of this journal (1949). In this paper it was shown that, as those abnormalities of man which are actually known in homozygous state and which appear to be recessive have become subjected to intensive study by the more delicate modern methods, more and more of them, such as thalassemia, sickle cell anemia, epilepsy, etc., have been demonstrated to leave distinct traces of their effect on the heterozygote.

In this connection, however, a difficulty arises for the supposition that the effect in the heterozygote is sufficiently detrimental to cause a selection against the gene. For a few of these superficially recessive conditions, of undoubtedly detrimental nature when homozygous, have proved to have so high a frequency in certain populations as to appear to require either an inordinately high mutation frequency or a slightly advantageous action when heterozygous, as compared with homozygous normals. Among these are thalassemia major in Mediterranean countries, sickle anemia in Africa and amaurotic idiocy in Sweden. As the interpretation of positive selection of heterozygotes seems more probable, the question arises as to how common this type of effect, sometimes referred to as "overdominance," may be. For, if abundant, it would work in direct opposition to the effects of ordinary dominance which have been considered above, and would seriously disturb our main calculations.

In regard to this question, it may in the first place be remarked that such cases of the phenomenon as do exist would, in consequence of the effect on frequency which they involve, become unduly conspicuous, and would thereby tend to give the impression of having originated more frequently than was actually the case. Secondly, it should be recalled that the above mentioned tests of recessive lethal and deleterious genes, both by Stern and Novitski and by the author and Campbell, gave definite evidence that, in *Drosophila* at any rate, the great majority of genes harmful to the homozygote, when picked up as mutants soon after their origination, are in fact disadvantageous to the heterozygote also. The same conclusion is to be drawn from the gene dosage and dosage compensation studies. There are, to be sure, contrary claims in *Drosophila* (Masing, 1938, 1939; Dubinin, 1946), as well as in some plant material, but careful scrutiny of the published reports indicates that in these cases adequate precautions were not taken to avoid complications due to ordinary heterosis. That is, the homozygous "normals" studied are likely to have been homozygous at the same time for more invisible detrimental genes than were those individuals which were heterozygous for the primary gene in question.

Looking at the matter from a more theoretical standpoint, it is to be expected that, despite occasional cases of mutant genes which happen, under certain conditions at any rate, to give the heterozygote a net advantage over both the normal and the homozygous mutant, the general run of mutant genes would give a detrimental effect in the heterozygote, similar to but lesser than that shown in the homozygote. That is, the heterozygote would tend to deviate from normal in the same direction as the homozygote, and the grade of detriment would tend to be proportional to the amount of this deviation. To suppose otherwise would involve the postulate that a deviant of minor degree is very often better adapted than the normal type. This is improbable except in the case of characters that are still becoming adapted to a condition which is new for the species, in terms of evolutionary time, or, what is much the same thing, to a condition that is local in its incidence on the species. For, except in special cases of balanced polymorphic types, any given character tends to become stabilized at a normal value that is optimal for the long-term conditions, so that only the very rare mutant, even if small in its homozygous effect, will succeed in being advantageous at all. And where, along the evolutionary track, some mutant gene did arise which was advantageous in its heterozygous degree of expression but deleterious homozygously, that gene, though temporarily multiplied as a make-shift arrangement, would usually have become replaced, after a while, by mutant genes of less deviant expression, occupying the same or other loci, which gave an equivalent advantage when they were present homozygously. For such genes would make possible a more uniform, and therefore (when all individuals were averaged) a closer approach to the adaptational optimum.

The reservation must of course be admitted that in civilized mankind the conditions of living have become so consistently transformed as to make many old optima out-of-date, thus opening the way for relatively many deviations formerly damaging to be advantageous. This makes it more likely now than in times past for some mutant genes of man which are still so extreme as to be detrimental when homozygous to be somewhat beneficial in their heterozygous expression. Nevertheless, even now such mutations must be far less frequent in origination than are those which are detrimental both to the homozygote and (roughly in proportion to their degree of expression in him) to the heterozygote. For there must always be many more disadvantageous kinds of change than advantageous ones, especially in a very highly organized system. And even when the system has become somewhat maladjusted in relation to its surroundings its complicated internal inter-adjustments would still cause the great majority of its individually taken blind steps of alteration, even those of slight degree, to result in its less harmonious operation. We may therefore, in view of all the above considerations, regard the great majority of mutant genes, even in man of today, as having a detrimental effect not only homozygously but also heterozygously, insofar as they manifest themselves at all in heterozygotes. Moreover, there are, as we have seen, cogent reasons for concluding that they do usually have a significant degree of heterozygous manifestation in man, probably at least as much as in *Drosophila*.

10. The effectiveness of dominance for slightly detrimental genes.

We have seen that where the degree of dominance of a lethal or near lethal gene is 2% or greater, as is usually true in *Drosophila*, the factor d of the expression $n = d\mu$ may be taken as nearly equal to 2, and similarly we may take $f = 2\mu p$, just as if dominance were complete. That is, such genes would be "effectively dominant" even if their measured degree of dominance were as low as 2%. Most mutant genes, however, are not lethal or nearly lethal when homozygous but exert a lesser amount of detrimental action. And the mathematical relations are such that, given the same degree of dominance, a less detrimental gene has a lower value of d than does a more detrimental one. It will therefore be necessary to give some attention to this point, in order to find out whether it needs to be taken into account, when expressions involving d are used for ascertaining frequencies of elimination and amount of damage in human populations.

The reason that less detrimental genes of a given grade of dominance attain a lower "*effective* dominance" in the population (i.e. a lower d), is because their higher persistence (p) leads to a higher equilibrium frequency (f), and therefore to a higher ratio of homozygotes to heterozygotes in the population (according to the Hardy-Weinberg formula, either modified or not modified by inbreeding) than in the case of genes which are more detrimental when homozygous but have the same grade of dominance. However, we have calculated that, for genes with a dominance of only 2%, the value for i_{ho}, the degree of impairment caused in the homozygote, has to sink to as low as about 5% (survival value, s_{ho}, 95%) before the elimination and the damage done to a large panmictic population in homozygotes becomes greater than that in heterozygotes. And with a dominance as high as 5%, the homozygous impairment, i_{ho}, would have to be as low as 1% (survival of homozygote 99%), before the homozygous equalled the heterozygous damage. For more general formulae dealing with these relations the reader may be referred to the paper now in press by the present writer and S. L. Campbell, previously referred to.

It is however very likely that the dominance would be even higher than 5% for most genes so slightly detrimental ($i_{ho} \leqslant 1\%$). For, on any selectionist interpretation of dominance, those normal genes whose mutations give only slightly detrimental effects would have undergone proportionately less selection for high potency on the part of the normal gene. Thus the mutant genes with less extreme effects, except when alleles of those with strong effects of the same kind, and also (though not so markedly, because of developmental correlation) the less extreme aspects of pleiotropic mutants, would tend to show even more dominance than that found for lethals and near-lethals. Dobzhansky's striking findings (1927) of the greater dominance of a whole series of mutations of *Drosophila* in respect to their slight, hidden effects on spermathecal shape than in respect to their conspicuous effects on pigmentation or other external characters, is an illustration of this principle in *Drosophila*. So too are the findings of a noteworthy degree of dominance on the part of many genes with effects so slight that they act perceptibly only as "specific modifers" of other mutants, less stable than the normal type, such as Beaded, Truncate, Bar, eosin, etc.

We are thus led to the conclusion that the great majority of mutant genes, even of those exerting only a slight degree of homozygous impairment, i_{ho}, are "effectively dominant." That is, d may in practice be taken as nearly 2 for mutations in general.

11. Minimum and maximum values for selective elimination in man.

Returning now to the question of the equilibrium frequency of selective elimination of individuals in man, we shall substitute 2 for d in the expression $d\mu_t$. Then, taking the minimum or "most conservative" value, 1 in 10, or 0.1, for the total mutation rate, we find the rate of elimination of individuals (or n_t, the rate of appearance of new cases) to be at least 1 in 5, or 0.2, as thus reckoned. There should however be some allowance here for "overlapping" of the incidence of elimination since we are now dealing with values above 0.1 (see p. 121, including footnote 6) and this would make the real value slightly smaller than 0.2 (about 0.182 on a random distribution).

It is interesting to note that the maximum possible value for eliminated individuals could not be more than about five times this minimum. That is, it could hardly be above 1.0 as reckoned by the approximation method (that in which correction is not made for overlapping). The figure 1 as so reckoned would really mean an average of 1 "occasion" for genetic extinction per individual, but the occasions would of course be distributed pretty much at random instead of being a constant of 1 per individual and there would therefore be some individuals who escaped elimination. Reference to the Poisson tables shows that in a random distribution averaging 1 per individual slightly over a third (.37) of the individuals would escape genetic extinction, nearly two-thirds (.63) being eliminated. But the rate of multiplication of mankind is surely not great enough, considering the high pressure of extrinsic causes of death (including infanticide) in the less civilized communities and the artificially low birth rate in the more civilized, and even in some primitive ones, to make it possible for even fewer than a selected third of that already reduced portion of the population which has escaped "accidental" death or sterilization to reproduce all of the next generation with undiminished population size. For this would require the selected fraction to much more than triple their own numbers in each generation. It is for this reason that we conclude that a value of 1.0 for the expression $d\mu_t$ must be a maximum.

If now we assume the above maximum to be the actual value for the frequency of elimination of mutant characters, letting $d\mu_t = 1$, and if we then substitute 2 for d, we obtain $2\mu_t = 1$; that is, $\mu_t = 0.5$. It will be seen that this value for μ_t is only slightly higher than that, 0.4, which was proposed as a "high" possibility on p. 128. Thus it seems very likely that the total mutation rate in man lies somewhere within the range between 0.1 and 0.5. In correspondence with this, the average frequency of newly arisen mutant characters (manifestations) per individual, n_t, would be between 0.2 and 1.0, and the extinction frequency at equilibrium would be not very different from this.

It will be a matter of the greatest importance, in the future, to obtain evidence which will make it possible to ascertain the values in question more exactly. For they are in any case so high as to be near the "critical level" for the species (see p. 155), a level in the neighborhood of which slight differences in these rates may tip the scales of biological consequences very far in one direction or the other.

12. The incidence of mutational impairment in man.

The values above arrived at are concerned with mutations on their first and last appearances only. The figure for f_t, the total frequency of manifestation of genetic impairments at equilibrium, must of course be much higher still. An estimate of it may be obtained by means of the simple approximation $f_t = 2\mu_t\bar{p}$. As we saw in section 5, $\bar{p}$ represents the average persistence, and the use of the coefficient 2 is even more justifiable here than in the expression $2\mu_t$ for last appearances.[7] The formula probably gives a minimum value for f_t because a positive correlation between the values of μ and p for the individual loci would cause the true value of $2\Sigma(\mu p)$ to be somewhat higher.[12]

In order to apply the above formula it is necessary first to arrive at a reasonable, or at least a conservative, estimate of the average persistence. Assuming the mutants to be effectively dominant, the persistence of each mutant will be determined almost entirely by the amount of impairment caused in the heterozygote, being the reciprocal of the latter, and this heterozygous impairment will be the product of i_{ho}, the homozygous impairment, by the per cent of dominance. Thus the higher the dominance the lower the persistence and we shall get a conservative (low) value for p by assuming the average dominance to be relatively high. Taking the dominance as 5% we find that, for each gene,

$$p = \frac{1}{.05\, i_{ho}} = \frac{20}{i_{ho}}$$

[12] Theoretically, it would be well to limit application of this expression to mutant genes having a persistence below, say, 1,000 or 10,000, or at any rate below the range in which elimination is so small, in relation to the pressures of mutation, drift and other accidental causes of differential multiplication, that the tendencies to equilibrium would cease to be effective. Practically, we are far from having enough knowledge of these factors and of the frequency-distribution for i to enable us to say just where such a line should be drawn, or to assess the amount of its effect, if drawn at one or another level, on the calculated f_t value. Nevertheless, because of the high frequencies which genes of such slight degrees of detriment attain, the value of f_t must be very greatly influenced by the precise level at which the line is regarded as being drawn. We have tried to stay on the ultraconservative side by disregarding genes with grades of detriment (i_{ho}) below about 10%, and supposing that there is no rise in frequency of origination of genes as the very slight grades of detriment are approached.

If we now suppose that incompletely lethal and detrimental mutations are equally distributed throughout all grades of i_{ho} from i_{ho} = almost 1.0 (almost completely lethal genes) down to $i_{ho} = 10\%$ (genes with a homozygous survival value of 90%), it can readily be reckoned that the p values of all these mutations taken together would average about 60 generations.[13] The complete lethals would have $p = 20$ if their dominance also is assumed to be 5%. As we have seen previously they are in flies a fifth as numerous as these detrimentals. When the p values of these two groups are averaged together (weighting detrimentals five times as heavily as complete lethals to correspond with their greater frequency of origination), the combined average for p turns out to be about 53 generations. If, as may well be the case, the dominance of genes of relatively slight grades of detriment is considerably higher than the 5% here assumed, this circumstance would tend to make the average p lower than here calculated. On the other hand, we have not included in our present reckoning the genes having i_{ho} in the 0 to 10% range. Even if these "slight detrimentals" had a dominance as high as 50%, and even if we still failed to include in our reckoning those with i_{ho} lower than 0.1%, nevertheless this group would tend to raise the average p considerably, provided there were as many mutations in this range as in the other ranges having an equal arithmetic latitude of i_{ho}.

However, studies carried on in *Drosophila* during the past year by Meyer, Edmondson, and the writer[14] indicate that in this organism the assumption of an equal distribution of detrimental mutations throughout all i_{ho} values (when represented on an arithmetic scale) does not hold. Instead, it appears that, following the high but descending peak formed by complete lethals ($i_{ho} = 100\%$) and nearly complete lethals (i_{ho} between 98% and 100%), there is a marked drop in the frequency of mutations. The mutations studied were induced in an autosome (the second chromosome) by ultraviolet light acting on an interphase stage (in the polar cap). Along with 208 complete lethals there were 20 mutants found in the range of i_{ho} between 98% and 100%, and again only 20 in the range of i_{ho} between 90% and 98%, although this range is four times as wide as the preceding one. If the rest of the distribution, as far as $i_{ho} = 10\%$, had only the same frequency of mutations as in the range between 90% and 98% there would have been only 240 detrimentals in the entire interval between 100% and 10%, to set against the 208 complete lethals found. But since we know from other work, previously cited, that the detrimentals in this interval are in reality several (about 5) times as numerous as the complete lethals

[13] Since the average p is proportional to the average of the *reciprocals* of i_{ho}, that is, to the harmonic mean of i_{ho}, it turns out to be much larger than if it could be obtained from the reciprocal of the arithmetic mean of i_{ho}.

[14] The work referred to in the above paragraph was supported by a grant from the U. S. Public Health Service, Division of Research Grants and Fellowships, given on recommendation of the National Cancer Council.

it is evident that their frequency must, at lower degrees of detriment (lower i_{ho}), rise very much above that existing in the 90% to 98% range. The distribution of frequencies of i_{ho} therefore forms a bimodal curve with one peak at the left origin, lethality ($i_{ho} = 100\%$), and another peak somewhere to the right.

Little more than this is yet known definitely about the shape of the curve in question, important though this genetic question is. However, there are grounds, both theoretical and observational, for regarding it as very unlikely that the second peak is near the first or that the rise towards it is sharp. Hence it is probable that detrimental mutations, instead of having an even distribution with respect to values of i_{ho}, form a curve which, except for its peak of near-lethals at the left end, is massively skewed towards the right, with its mean at a value of i_{ho} significantly beyond the middle (0.5). If this is true, it would have the effect of making the average value of p a good deal higher than the above estimate, 53 generations, which we reached by assuming an equal distribution of detrimental mutants among all values of i_{ho} down to 10%.

Despite the above considerations indicating that p probably has a value a good deal higher than 50, we have decided, in the interests of caution, to assume for purposes of our discussion that it is only 40. This is the value which would obtain if all mutant genes exerted a homozygous detrimental action, i_{ho}, of 50%, exactly in the middle of the range of possibilities, or if the harmonic mean of i_{ho} were 50%, and if at the same time the average dominance were 5%. In the author's opinion the harmonic mean of i_{ho} is probably much less than 50% but on the other hand the dominance may average much more than 5% in man, especially when the lesser detrimentals are considered, and there may be a considerable negative correlation between i_{ho} and dominance which also would tend to reduce p. There is, it should be realized, such a lamentable paucity of numerical data for human beings, or for any vertebrates, of a type which would throw light on the actual values of these factors, that we cannot feel too secure in regarding even 40 as a lower limit for p. It is to be hoped, however, that a discussion of the implications of a presumptive set of values will point up the importance of the quantitative problems at issue. Hitherto there has been far too little awareness of the existence—let alone of the theoretical and practical significance—of these problems as actual subjects of numerical inquiry. Moreover, the very fact that the attack on them will be so difficult and laborious makes it the more desirable for them to be visualized as clearly as possible.

If now we substitute 40 for $\bar{p}$ in our equation $f_t = 2\mu_t\bar{p}$, and at the same time take the most conservative estimate of μ_t for man, namely 0.1, we find $f_t = 2 \times 0.1 \times 40$, an expression which reduces to 8. This would mean that each individual, on the average, carries 8 slightly dominant, detrimental mutant genes in heterozygous condition. The numbers of individuals carrying different numbers of these genes would then tend to form a Poisson series, having 8 as its average. On the whole, those individuals who died the genetic deaths would simply be that fifth of them who, on the whole, carried a more detrimental assortment of these genes, and they would average only about one more detrimental gene per individual than the others.

In the above reckoning we have purposely left out of account those genes, very high in their frequency in the population yet very rare, relatively to the others, in their origination, which are of virtual indifference for survival. Although we would be unable to say at just what level of i_{ho} this line should be drawn, and it must in fact be a "cline" rather than a line, nevertheless we have certainly erred far on the side of caution, by excluding from our reckoning a host of genes of slight yet definitely detrimental action (see footnote 12). Likewise we omit from the reckoning those genes which are positively maintained by a balanced selection, at a level short of "fixation," because of the limited advantage they confer under special conditions. In such cases the advantage maintains the balance by becoming smaller per individual, and finally turning into a disadvantage, the more the number of individuals having the character rises. It is these two classes of genes, chiefly the relatively indifferent and to a lesser degree the balanced, which contribute so largely to the superficial genetic polymorphism of any human population, as well as to its polymorphism in such cryptic characters as the common blood antigens.

Now how important are these 8± detrimental genes to us and what are their effects? Each of these genes, at this first approximation, has an average selective disadvantage of one-fortieth, or 2.5%. Therefore, the 8 of them, considering them as roughly cumulative, or rather, as having synergistic at least as often as compensating disadvantages (which would surely be the case on the whole), must give an average grade of detriment of about $\frac{1}{40} \times 8$, or $\frac{1}{5}$; that is, 20% disadvantage. Of course, we could have arrived at this result more directly because the figure of 20% average disadvantage is necessarily the same as the average chance of genetic extinction of an individual. We now see however that, because of the multiplicity of mutant genes per individual, the detriment and the risk are a good deal more evenly distributed through the population than we might have imagined. Even on this conservative estimate, then, most of us have a nearly 20% chance of death or of reproductive inefficacy, from genetic causes. Or rather, this would have been true if we had lived under those comparatively primitive conditions which until recently prevailed for some thousands of years, and to which a rough genetic equilibrium must have become established. That is, the average man must be in one way or another, all told, at least 20% below the par of the fictitious all-normal man.

13. How the genetic load is usually felt.

Some may believe that this much encumbrance, usually divided up among so many little shortcomings, must be practically negligible. For example, Haldane (1939*a*) has stated that "we are only concerned with cases where f [the survival rate, as here used] lies between . . . lethality . . . and . . . 10% disadvantage. For genes with a value of f very close to unity are practically harmless to the individual, whatever may be their social disutility." Others of us, including the present writer, feel, on the contrary, that even a 10% risk of any kind of death or extinction is a very sizeable danger. Few persons would be free from misgivings if they had to undergo an operation, to take a trip, or to contract a disease, with this amount of risk. Moreover, they would probably feel keenly the load of a handicap or combination of handicaps that reduced their expectation of perpetuation to this extent, if this load were suddenly put upon them, although if brought up with it they would doubtless have become insensibly inured and resigned to it, even as a congenitally blind person may remain largely oblivious of his infirmity. But to argue that unawareness of a misfortune makes it unimportant is, in principle, no more valid in the case of other genetic disabilities than in the case of blindness.

We tend to carry our burden more or less unconsciously at first, and then for a time rather zealously like Christian in *Pilgrim's Progress*, but we usually become more weighed down by it in our later years, as all our powers gradually dwindle. The inadequacies in those physiological systems that happen to be weaker in us usually become noticeable first. Hence this person develops rheumatism prematurely, as we say, that one is more prone to cancer, and a third to high blood pressure or nervous tremors or loss of memory, or merely of his good disposition. Again, even in youth, in times of greater stress, as in war or other over-exertion or during and after attacks of disease, a person's individual limitations are more likely to come to the surface, although often the victims themselves will consider the cause of all their trouble to lie in the adverse circumstances. Each, however, presents his characteristic pattern of inadequacies or weaknesses, and these patterns tend to run in families. But the fact that patterns of culture and habit, and even material goods, also run in families, makes the tangling of the genetic with the non-genetic the more intricate and confusing.

It is to be expected that most of these manifestations of heterozygous mutations would appear only as small quantitative differences. For, in the first place, nearly all observed characteristics depend upon many genes. Most of these genes act more or less cumulatively, as "modifiers," so that a change in any one of them usually affects the result only slightly, even when homozygous. Secondly, most mutant genes act, when homozygous, like feebler editions of their own normal alleles: they are, as we say, "hypomorphic," and therefore cause changes of degree. Thirdly, the genes in their heterozygous state usually cause a much lesser degree of deviation than when homozygous. For all these reasons, then, the individual heterozygous for a number of mutant genes would be subject chiefly to exaggerations of the same kind of troubles as even the most normal man might have; in fact, the latter also would at times show them to the degree in question, when he happened to be exposed to somewhat more adverse conditions.

Thus these genetic effects are by no means to be distinguished readily from the effects of trying environments: of dietary deficiencies, chronic infections, exposure, overwork and so forth. And undoubtedly the two sets of factors, genic and environic, interact most intimately in the production of the observed results, so that the ailments are to a large extent combination effects. It must often happen, moreover, that the symptoms of the genetic shortcomings, especially when less complicated by unfavorable outer circumstances, are so subdued, vague and hard to diagnose as to lead physicians in their professional capacity to ignore them, as not worth bothering with, and/or to conveniently dismiss them as hypochondria on the part of the patient. Yet improvements in living conditions as well as in medicine in general have in modern times resulted in an ever decreasing intensity of these afflictions, for the generations immediately involved, especially when the age of the individuals involved is also taken into account. At the same time, however, diseases and injuries of more strictly extrinsic origin are becoming much more drastically reduced than these, and the average length of life is being greatly increased. Under these circumstances the differences due to genetic ailments, despite their mitigation, stand out ever more conspicuously by contrast.

We see that, in mankind under present circumstances, these heterozygous genetic weaknesses, when in a setting of favorable external conditions, are seldom to be classed as outright "diseases." In view of this, we might in a very limited sense agree with the statement quoted in our introduction, that "mutation as a direct cause of disease is extremely rare and of little practical significance." This situation is however due to the fact, so fortunate for all of us in this generation, that our germ plasm was selected, in our more primitively-living ancestors, for a world without central heating or refrigerators, without labor-saving mechanisms in the home, in industry or in agriculture, without sewers or bathrooms, and without knowledge of contraceptives, asepsis, antibiotics, calories, vitamins, hormones, surgery or psychosomatic treatment. And so now for the first time, with the newly found aid of all these devices and methods, the average American, in spite of his eight or more inborn disabilities, adding up to at least a 20% natural disadvantage, manages to get by for almost the three score and ten years which, surprisingly enough, ancient tradition declared to be the "normal" span.

14. The penalty for relaxing natural selection.

In view of the considerations adduced in the preceding section, the question now arises: granting this inborn disadvantage which would amount to at least 20% under primitive conditions, may we not regard this as relatively unimportant under our present conditions of living? Furthermore, may we not confidently expect that, with continued advances in general technology, living standards and medicine, the genetic burden will be further lightened and kept very small indeed?

Certainly there is no use in getting morbid over our own natural shortcomings, and it is best not to dwell upon them but to take what steps we can to ameliorate them. Their really scientific diagnosis and treatment is, to be sure, a very recondite and elusive matter indeed, for a surprisingly high proportion of persons, because of the fact that there is such a multitude of different kinds of hereditary ailments, each individually so rare, yet in their collectivity so frequent. Medical men will discover this when they come to take these disorders more seriously and they will then recognize once more that familial complaints, which will then be the main complaints, call for physicians who take the characteristics of the entire family into consideration. In consequence, the pressure of the mutational load will be reduced even more, for the generations immediately treated.

The great trouble with this method is that if (as today) it is unaccompanied by artificial selection it passes down to an indefinite number of future generations the burden that it has spared the treated generation itself. Of course these later generations can be treated in turn. But each successive generation will have not only the mutant genes which have in this way been passed along to it but also its own new crop of mutations. Thus the number of mutant genes will increase unless and until we again let as many die out as arise. To put the matter in other words, if our ameliorative procedures succeed they must inevitably (barring conscious selection) cause a smaller number of mutant genes to be reproductively eliminated per generation than were eliminated originally. In fact that is today one of the main aims of these procedures. But the number eliminated originally (under primitive conditions) must have been the equilibrium number, i.e. equal to the number of new mutations arising. The number eliminated when ameliorative treatments are given is therefore less than the number of mutant genes arising. Thus the conditions for the application of the basic equilibrium theorem, $f = np$, have been violated. For we have diminished i, thereby increasing p, and causing a rise in f.

The rise in f_t, the total frequency of manifestation of mutant genes, must inevitably continue, so long as these circumstances continue, until at last its value becomes so high that a new equilibrium is reached, at which the total frequency of individuals eliminated per generation is again equal to n_t, the total frequency of new cases arising. This means that despite all the improved methods and facilities which will be in use at that time the population will nevertheless be undergoing as much genetic extinction as it did under the most primitive conditions. In correspondence with this, the amount of genetically caused impairment suffered by the average individual, even though he has all the techniques of civilization working to mitigate it, must by that time have grown to be as great in the presence of these techniques as it had been in paleolithic times without them. But instead of people's time and energy being mainly spent in the struggle with external enemies of a primitive kind such as famine, climatic difficulties and wild beasts, they would be devoted chiefly to the effort to live carefully, to spare and to prop up their own feeblenesses, to soothe their inner disharmonies and, in general, to doctor themselves as effectively as possible. For everyone would be an invalid, with his own special familial twists.

But, it may be objected, medicine and technology in general will probably continue to make progress, so that after the centuries or millennia needed for getting near to a new equilibrium, adjusted to today's and tomorrow's techniques, the still more advanced methods of that time might be so well able to cope with the increased frequency of f_t as to allow people to suffer from no more net disadvantages, or perhaps even less, than at present. In other words, the equilibrium goal set by present practices would by that time be long out of date. And this would, it might be urged, happen repeatedly, in fact continuously, so that an equilibrium for mutant genes would never need to be arrived at and the advancement of technique would always manage to stay ahead of the mutational accumulation process.

The above view, espoused especially by persons with an antipathy to practical applications of genetics in man, is one of blindly optimistic faith in the omnipotence of artificially controlled environmental influences. Its fallacy is of the same kind as found in the view, put forward in kindred circles, that the Malthusian principle is entirely wrong because advances in physical and socioeconomic techniques will in the future enable us always to increase our means of subsistence faster than our population can naturally multiply. In both cases the nature and the enormity of the situation have eluded comprehension. It is not realized that the procedure proposed is, in the long run, as effective as trying to push back the flowing waters of a river with one's bare hands.

If the attempt were made to continue indefinitely to substitute a more remote equilibrium for f_t, by ameliorative practices, it would mean an ever greater heaping up of mutant genes. There would be no limit to this short of the complete loss of all of the genes or their degradation into utterly unrecognizable forms, differing chaotically from one individual of the population to another. Our descendants' natural biological organization would in fact have disintegrated and have been replaced by complete disorder. Their only connections with mankind would then be the historical one that we ourselves had after all been their ancestors and sponsors, and the fact that their once-human material was still used for the purpose of converting it, artificially, into some semblance of man. However, it would in the end be far easier and more sensible to manufacture a complete man *de novo*, out of appropriately chosen raw materials, than to try to refashion into human form those pitiful relics which remained. For all of them would differ inordinately from one another, and each would present a whole series of most intricate research problems, before the treatments suitable for its own unique set of vagaries could be decided upon.

Admitting this to be a *reductio ad absurdum*, our critics might object that no such unlimited continuance of mutational accumulation was intended, but only a reasonable amount of it, whatever that might prove to be. The answer to this is that unless the practice were indefinitely continued, there would be some stopping place (either sudden or gradual) and that, following this, elimination would after all have to be allowed to become equal in frequency to the new mutations, in order to prevent the still further accumulation of mutant genes. Now unless this "allowed" elimination were brought about by some type of artificial selection, as for instance by voluntary abstention from reproduction, it would mean that those who constituted the proscribed quota—which we have seen to be at least 20% of the population—were, as in early times, dying out as an automatic consequence of their own inadequacy.

If then the eliminated 20% failed involuntarily—that is, despite all their own and their community's efforts, we may be sure that most of the remaining 80%, although they had contrived to reproduce would on the whole differ from the doomed fifth but slightly. That is, they would in the main be "marginal cases" who had managed to get along, even with the aid of the vastly improved techniques of that time, only barely and with difficulty. For these "successes" would in fact be encumbered with the great load of those additional mutations that had accumulated during the period in which equilibrium was being postponed. Practically all of them would have been sure failures under primitive conditions and their perpetuation now, after the reattainment of equilibrium, would be contingent on a continuance of the ameliorative practices at that new level of intensity which corresponded with the new equilibrium. This permanent requirement would be the heritage that had been bequeathed by "debtor generations" like our own. The term "debtor" is appropriate for such generations because, by instituting for their own immediate benefit ameliorative procedures which delay the attainment of equilibrium and raise the equilibrium level of mutant gene frequency, they transfer to their descendants a price of detriment which the latter must eventually pay in full.

It is very difficult to estimate the rate of the deteriorative genetic process which present practices occasion. No one knows how much less stringent selection is today, in any one particular, than it was in primitive times. But unless we take the naive position that ailments of genetic origin cannot be mitigated by artificial means we must admit that modern methods do result in the saving for reproduction of many mutant genes which otherwise would have been eliminated by the defects they produced. Thus, assuming only our 20% minimum value for the equilibrium frequency of genetic elimination, the fact that the average American now lives beyond 65 is a proof that nothing like the equilibrium quota is eliminated by death before the age of reproduction. This may also be deduced from the fact that an average number of children of not much more than two born per adult is at present about sufficient to maintain the population.

Moreover, we cannot assume that the elimination rate is brought up to the required level by means of a highly selective failure to reproduce on the part of those who live. For a very considerable fraction of those whose lines are dying out today are known to have followed this course more or less purposely, as a result of conditioned behavior that depended primarily upon circumstances of their mode of living, their experiences and their tradition, rather than upon undesirable genetic traits. Making allowance for this major, non-genetic contingent of the relatively "infertile," there must be much too little room left for reproductive selection in the multiplication of a population like ours, whose number of children per adult shows a variability so much smaller than in former times.

It is of course possible to calculate readily the rate of deterioration that would result from a given *assumed* amount of relaxation of selection, if values are also assumed for total mutation rate, μ_t, and for the average persistence, $\bar{p}$ (the latter being expressed in terms of the value which it would have had under primitive conditions). Let us, for instance, take the very moderate-seeming assumption that at present one half of those who would have been genetically eliminated in primitive times succeed in perpetuating themselves, and let us at the same time follow our previous assumptions, also chosen on the side of caution, that n_t is only 20% and that $\bar{p}$, for primitive conditions, would be as much as 40 generations. Using these values we find that the increased impairment of the next generation as compared with the present one would be $\frac{1}{2} \times \frac{1}{5} \times \frac{1}{40}$, that is, 0.25%. Examining this reckoning in detail, we see that each person of the next generation would on the average receive $\frac{1}{2} \times \frac{1}{5}$, i.e., $\frac{1}{10}$ of a mutant gene more than this generation had. And if the heterozygous impairment averaged, for primitive conditions, $\frac{1}{40}$ (i.e. 2.5% reduction in the individual's chance of perpetuation per heterozygous gene), the resultant *additional* average impairment per offspring would be $\frac{1}{10} \times \frac{1}{40}$, or 0.25%, from the standpoint of what the effect would have been under primitive conditions.[15] It is evident that if this rate of decline continued (it is much more probable however that, if the mores did not change, the rate of decline would

[15] Our assumption that the selective elimination has been halved implies however that under present conditions, including modern treatments, the impairment would on the average be only one-half as manifest as in primitive times. Thus there would be a lowering of present survival value (i.e. of survival value measured in relation to modern conditions) of only 0.125% per generation.

accelerate as techniques improved), it would take some 40 generations, a period of time of the order of a thousand years, to cause the amount of disability—as measured in relation to primitive conditions—to change from the equilibrium level of 20% to a level of 30%. And there would be a corresponding rise of f_t from the value of 8 to that of 12 mutant genes per individual.

It is very likely that the combination of values assumed above is a far too cautious one. For example, it is quite conceivable that not merely a half but even three-quarters of the genetically "proscribed" quota are now perpetuating themselves, that n_t, instead of being 20%, is approximately 100% (see page 138), and that $\bar{p}$ is, because of an exceptionally high dominance of mutant genes in man, only 8. In that case each individual of the next generation would on the average have ¾ of a mutant gene more than the individuals of this generation, and this would cause the average chance of survival, as measured in relation to primitive conditions, to have a decrement of ¾ × ⅛, i.e. of nearly 10%. In that case, if the average disability were 20% now, as measured in these terms, it would be raised nearly to 30% in the course of a single generation instead of in a thousand years. That this estimate of the change is almost certainly too high is suggested by observations on the similarity in strength, morbidity, etc. of the offspring of savages and of long-civilized peoples, or of upper and lower castes, respectively, when raised under similar conditions. However, it is doubtful whether most ancient and medieval civilizations were much more genetically sparing than conditions of savagery were, for the majority of the people. And certainly the past hundred years have seen more "progress" in this respect than all the past history of civilization. This makes it the more necessary now to carry out as exact comparative studies as possible, of the kind in question, so that we may be enabled to set an upper limit to our estimate of the possible rate of genetic deterioration. In the meantime, however, we must emphasize our uncertainty concerning the quantitative aspects of this matter, the need of further investigation of them, and the open possibility that the deterioration consequent on the present relaxation of selection may after all be a good deal more rapid than has commonly been imagined even by geneticists.

Whatever the values finally found, it is evident that the natural rate of mutation of man is so high, and his natural rate of reproduction so low, that not a great deal of margin is left for selection. Thus if μ_t has the minimal value of 0.1 (n_t = 0.18) an average reproductive rate of 2.4 children per individual would be necessary to compensate for individuals genetically eliminated, without taking any account whatever of all the deaths and failures to reproduce due to non-genetic causes. But when these are taken into account as well (even though we allow only that reduced number of them that occurs under our modern conditions) it becomes perfectly evident that the present number of children per couple cannot be great enough to allow selection to keep pace with a mutation rate of 0.1. If, to make matters worse, μ_t should be anything like as high as 0.5, a possibility that cannot yet be ignored, our present reproductive practices would be utterly out of line with human requirements.

15. The avoidance of the penalty.

Unless means could be found of lessening the natural mutation rate (a feat that would require the extended maintenance of the germ cells *in vitro* as a regular procedure), this rate presents a base line, an irreducible minimum, below which gene elimination cannot permanently be decreased. As shown above, attempts to do so can have only temporary success. We cannot eat our cake today and have it tomorrow. In later generations a genetic selection must be resumed which is in its essentials as rigorous as that which was necessary for the maintenance of equilibrium even under the most primitive conditions.

But to pessimists protesting "What price progress then?" it must be pointed out that there is after all one and just one way of avoiding the fiasco of a full fledged resumption of ordinary natural selection. That method, whether we like it or not, is purposive control over reproduction, exercised in such wise as to anticipate and forestall the need for natural selection of the usual, externally imposed type.

In order to fulfill the aim of achieving a form of selection more humane than that resulting from the unalloyed struggle for existence, it would of course be all-important for this purposive control to be carried out, not by means of decrees and orders from authorities, but through the freely exercised volition of the individuals concerned, guided by their recognition of the situation and motivated by their own desire to contribute to human benefit in the ways most effective for them. This is the only real solution, the only procedure consistent with human happiness, dignity, and security. For to be slaves coerced by others is even more obnoxious than to be exposed to the full rigors of nature. But for the voluntary adoption by people in general of a course of such wisdom, and so different from that now followed, a deep-seated change in mores would be necessary. Not least among the requirements for this would be a far more thoroughgoing and widespread education of the public in biological and social essentials (see p. 163). And there would also have to be very great improvement in the technical methods whereby the more important features of the genetic constitution may be judged.

Granted that such voluntary reproductive control can eventually become effective enough to result in the elimination of as many mutant genes per generation as concurrently arise through mutation, the ameliorative practices of medicine and of civilization generally are divested of all their harm to later generations. Strange as it seems, we can in that case both eat our cake and have it. Instead of boomeranging back to plague the future, our palliative procedures then become valid means whereby the individual here today, and in every successive generation, may without compunction roll off the oppressive load which heretofore has been ordained to all species in their struggle for existence. But this is possible only when the rational guidance of parenthood is given its place as the necessary complement to medicine and all other "euthenic" practices. It must be recognized that it is equally as necessary, in the end, as they, for the attainment of the very goals which they themselves seek. With either of these two legs missing, the body of mankind as a whole cannot continue to stand erect. But with both of them, and only with both of them, it can. Thus the exercise of a measure of prudence, in allowing reproductive practices to be influenced to some extent by the interests of those who are to follow, may at last gain a vast extension of well being and of freedom for everyone.

It has apparently not been realized that the guidance of reproduction, in the light of increased knowledge of human genetics, may eventually attain a level of proficiency such as to require, for the maintenance of equilibrium, a much smaller amount of selective elimination than is necessary in the course of ordinary natural selection. That is, although still subject to the principle that there must be as high a frequency of mutant genes eliminated as arise by mutation, mankind can nevertheless be released from the condition that the frequency of *individuals* meeting extinction must be approximately equal to n_t, the total frequency of newly arisen cases of manifestation of mutations. This apparent paradox arises from the fact that there is so much variability in regard to the number of mutant genes carried by different individuals of a population as to make it possible, by judicious and efficient picking of the individuals having the highest numbers of mutant genes, to find the necessary quota of μ genes for elimination in a much smaller proportion of individuals than 2μ. Although there is, to be sure, some tendency for this to happen even under natural selection, by reason of some combinations of mutant genes having synergistic (i.e. more than cumulative) detrimental effects, and for these genes therefore to become eliminated disproportionately often when in such combinations, nevertheless a really purposive choosing of the more heavily laden individuals could attain far greater efficiency in this respect than would happen naturally.

For the purpose of numerical illustration, let us first recall our previous calculations concerning elimination under ordinary natural selection, and then compare them with new calculations, dealing with the possibilities for rationally guided elimination. We have seen (p. 138) that if μ_t, the total mutation rate per gamete, is 0.1, and if the dominance is "effective," then n_t, the frequency of newly manifested cases per individual, is the same as the frequency of individuals eliminated at equilibrium under natural selection, and has a value only slightly less than 0.2, namely, 0.18, provided we assume (1) the independence of distribution and (2) the independence of detrimental action of the mutant genes. Although the second assumption is certainly inaccurate, as pointed out previously, nevertheless provisional consideration of the matter indicates that it is unlikely for the frequency and strength of synergistic action of mutant genes to be so great as to reduce the frequency of elimination from a value of 0.18 to below, say, 0.15.

When now we turn to the possibilities of intelligently directed selection we find the situation very different. In this case let us assume, as a limiting instance, that the individuals having the largest number of mutant genes are systematically chosen for elimination. Our mathematical problem now is to ascertain what fraction of the population would carry enough genes in excess of the average, 8 per individual, so that when this most heavily loaded fraction is subtracted the remainder of the population would have a gene frequency lower than the average by μ_t (0.1) per genome (0.2 per individual). To find this

TABLE 1

POISSON DISTRIBUTION WHEN m (THE AVERAGE VALUE OF x) IS 8.
(P = PROBABILITY OR FREQUENCY OF CASES HAVING THE GIVEN VALUE OF x.)

x	P	$P(x-m)$	x	P	$P(x-m)$
0	.000335	−.002680	13	.029616	+.148080
1	.002684	−.018788	14	.016924	+.101544
2	.010735	−.064410	15	.009026	+.063182
3	.028626	−.143130	16	.004513	+.036104
4	.057252	−.229008	17	.002124	+.019116
5	.091604	−.274812	18	.000944	+.009440
6	.122138	−.244276	19	.000397	+.004367
7	.139587	−.139587	20	.000159	+.001908
8	.139587	.000000	21	.000061	+.000793
9	.124077	+.124077	22	.000022	+.000308
10	.099262	+.198524	23	.000008	+.000120
11	.072190	+.216570	24	.000003	+.000048
12	.048127	+.192508	25	.000001	+.000017

fraction, we shall for approximation purposes assume a Poisson distribution and consult Poisson tables. It is not likely that, under natural selection, and with the mating system largely random so far as defective genes are concerned, the departure from a Poisson distribution would be serious, although there would even in this case be some reduction in the frequencies of individuals with higher numbers of mutant genes.

In these tables, the condition $m = 8$ would correspond in our own example to there being an average of 8 mutant genes per individual. Thus m may be equated to our symbol f_t. We have listed in table 1 the values which obtain in that case. Here the actual number of mutant genes carried by an individual is represented as x, in the first (leftmost) column. In the next column, the values shown, which we have designated as P, tell what proportion of the population carries exactly x mutant genes, under the given condition that the average of the x's of all individuals is 8. In the third column we have shown the values of the product $P(x - m)$. This expression tells us what *excess* fraction of the mutant genes of the entire population is carried by the group having exactly x genes. That is, it is the fraction of the whole population's genes which they carry, beyond that quota of 8 genes per individual which represents the average for the whole population. Beginning with the bottom row (largest x), and proceeding upwards, we may then add together the values of $P(x - m)$ up to the level at which this sum, if divided among the *remainder* of the population, would become equal to 0.2 ($2\ \mu_t$). A little trial shows that this procedure takes us up to about six-tenths of the way through the row for $x = 14$. The sum of the $P(x - m)$ values up to this level is 0.196, and the remainder of the population, gotten by summing the values of P above this level, forms 0.973 of the whole. Dividing the first figure, 0.196, by the second one, 0.973, we obtain 0.20. This means that the excess of genes carried by those groups having x from 14 to 25 (but including only 0.6 of those with $x = 14$) would if distributed evenly over the remainder of the population, raise its mutant gene content by an amount equal to $2\mu_t$ per individual. Conversely then, the remainder of the population must have a deficit of the desired amount, namely 0.20 genes per individual, below the average, otherwise all the population together would not average m genes. Hence the subtraction from the population of that contingent of groups whose genes are in excess of the level in question leaves a remainder with a mutant gene frequency just enough below the average to compensate for the gain in mutant genes which is caused in one generation by the mutation rate of 0.1 in the germ cells of both sexes.

It will be seen that the contingent having the excess of genes required for balancing against the mutation rate constitutes (as found by adding its P values) only 2.74% of the entire population. Thus, theoretically at least, a rise in the mutant gene frequency of the next generation as compared with the present one could be prevented from occurring by the elimination from reproduction of less than 3% of the potential parents, instead of the 15 to 18% demanded by natural selection, provided the number of mutant genes per individual could be exactly ascertained. Similar calculations made on the basis of the more extreme assumptions dealt with on page 138 ($\mu_t = 0.5$) show that in that case the non-reproducing fraction of the population would be reduced from the 0.6 or more demanded by natural selection (see p. 138) to somewhat less than 0.2 when guided.

It should be noted, however, that the above calculations apply only to the selection required in the first generation in which guidance is exercised and that later the non-reproducing quota has to be raised somewhat. This is because the systematic elimination of the highest gene concentrations in each successive generation leads to a departure from the Poisson distribution, skewing the actual distribution towards the lower gene concentrations. This makes it necessary later to eliminate a somewhat larger fraction of the population in order to attain the same amount of gene elimination. The calculation of the amount of selection finally necessary, and of the curve of approach to this constant value, would be a lengthy and intricate matter, but it is to be hoped that some one will undertake it. Meanwhile, it is evident that even when stability in this respect has been reached, the elimination required under the system of guided selection would still be much smaller than that demanded by ordinary natural selection. Moreover, it is reasonable to expect that, although far from complete accuracy in estimating mutant gene number can be achieved in the foreseeable future, nevertheless the advance of genetic knowledge should make possible a considerable reduction in the amount of elimination necessary for maintaining equilibrium, if such knowledge were made use of in the guidance of reproduction.

We have in the above treatment, for the purpose of simplification, taken account only of the numbers of mutant genes, without regard to their relative injuriousness ($1/p$). From the phenotypic viewpoint, more efficient selection, in the sense of selection causing a greater lightening of the phenotypic load per individual, would of course be attained by taking this factor also into account, but the consideration of this matter would take us too far afield here. Suffice it to say, however, that tests could probably be carried out more readily, in actual practice, for estimating the load in terms in which this factor did enter into the reckoning, than for estimating merely the mutant gene number by itself, as above postulated. At the same time, although the fraction of individuals to be eliminated would be increased by attaching this additional condition,[16] the general principle would remain that selection based upon such knowledge would make possible the maintenance of equilibrium by means of the elimination of a smaller contingent of individuals than that required by ordinary natural selection.

16. The effect of a long-term increase in the mutation rate.

The formula for equilibrium frequency, $f_t = 2\mu_t\bar{p}$, shows that the genetic load carried at equilibrium is directly proportional to the mutation rate. Therefore, if other factors remain constant, the permanent raising of the mutation rate to a given, moderate multiple of its former value (such as, say, 1.25 or 2 times) eventually causes, by the time equilibrium is reached, the same rela-

[16] It might however be judged preferable to pay attention more especially to gene number, disregarding in part at least the amount of gene effect, since this procedure would require a smaller amount of elimination for the maintenance of equilibrium. For the increase of phenotypic load thereby resulting might, when coupled with ameliorative procedures, be considered less important than the advantage of having a smaller elimination requirement. This point of view would be quite legitimate, and not in contradiction to that previously set forth, since we are here assuming that in any case there will be enough selection to maintain equilibrium, i.e. to prevent an unlimited rise in the load.

tive rise (to 1.25 times, twice, etc., as the case may be) in the frequency of mutant genes present. *Pari passu,* there is of course the same relative rise in the total pressure of genetic ailments on the population, and in the frequency of individuals meeting genetic extinction. If, as we have seen reason to conclude, even the present genetic load is a serious one, then its increase by only 25% (i.e. to 1.25 times its present value) would be a matter of grave consequence, while its doubling would approach the calamitous.

This becomes the more evident when we consider that, as explained in section 14, our ameliorative practices are at present allowing us to feel only a fraction of the genetic load but that in time, as the new equilibrium values are reached, we must despite all ameliorative measures come to feel the full force of this load again, a force as great as that in primitive times—unless conscious selection has in the meantime been resorted to in order to keep the equilibrium frequency down. Hence, if and when the stage is attained which we are now headed to, the "25% greater load" caused by a 25% rise in mutation rate will not mean a load that is 25% greater than the *present* one, but 25% greater than the load which would otherwise have come into existence by that time, and which would by itself have been equivalent to the load of primitive times. On the other hand, if the load had been kept down by conscious selection, then the 25% increase occasioned by the rise in μ_t, although far less evident phenotypically, would nevertheless demand an amount of selective elimination which in each generation was 25% higher than would otherwise be necessary.

The consequences above described are to be expected from a rise in mutation rate only if the condition has been adhered to that this rise is of moderate size. This qualification arises from the fact, previously pointed out, that the "normal" human mutation rate is at best not very far from the upper limit which natural selection, even that of primitive times, is capable of coping with. Thus, if μ_t should rise above 0.5, the amount of selective elimination required for the maintenance of equilibrium would, as we have seen, be greater than the "rate of effective reproduction"[17] of even primitive man would have allowed. Hence equilibrium could not be maintained, and the genetic composition would deteriorate continuously, while the population would meanwhile diminish in numbers all the way to the point of disappearance. In the case of a population in which, as in many civilized nations, the birth rate is held down to an average of not much more than two per family, the upper or critical mutation rate, that beyond which any equilibrium is impossible, must be much lower than 0.5 and, as we have seen, perhaps lower than 0.1, even if natural selection were, within

[17] The rate of reproduction theoretically remaining after all cases of death and failure to reproduce of purely non-genetic causation have been subtracted. In a population at genetic equilibrium and constant in numbers this effective rate must be equal to 1 plus the proportion that meets genetic extinction, i.e. approximately $1 + n_t$ (provided n_t is low enough so that overlapping of the extinction effects can be ignored).

the limits set by these conditions, to be given full scope. Since however it is not being given anything like full scope at present, we are not maintaining equilibrium anyhow, and under these circumstances any increase in μ_t will simply accelerate, to a corresponding degree, the decline that must already be going on. If now we postulated that the conditions of raised mutation rate, low birth rate, and lack of conscious selection were all to continue, it would be very problematical whether or not this decline would eventually be arrested by the rise in mutant gene frequency, f_t. Although ordinarily this internal checking mechanism must finally come into play to force a resumption of elimination at the equilibrium level, the answer to the question of whether the rise in f_t would in this case be sufficient to stop the decline would depend upon the very fine point of whether or not the mutation rate had been raised above that level which, at the given rate of reproduction, was "critical," in the sense defined above.

At present our quantitative knowledge of the factors concerned is far from precise enough to enable us to deduce just what the critical rate would be, for any given rate of effective reproduction. Thus we can only say that even a moderate rise in mutation rate might, conceivably, if continued indefinitely under conditions like those now existing, be sufficient to spell the difference between the maintenance and the extinction of the population.

17. The effect of a short-term increase in the mutation rate.

Despite the magnitude of the effect of a long-term increase in the mutation rate, discussed above, it is so slow in its onset that, when observed over the course of but a few generations of ordinary, largely random, breeding, it is likely to be imperceptible. To illustrate this, let us attempt to estimate the amount of effect which a given rise in the mutation rate of one generation, of an amount not improbable in human beings, would produce in the immediate offspring. For this we may take the figure for mutation rate previously proposed as "conservative," namely $\mu_t = 0.1$, and then suppose that it is raised by 50% of its own value, i.e. from 0.1 to 0.15. The amount of this rise, 0.05, is approximately that which would be induced by treatment of immature germ cells of *Drosophila* with an X-ray dose of 100 r, although in *Drosophila* this doubles μ_t, since the natural rate for *Drosophila* is only 0.05.

Now this 0.05 rise in μ_t will cause 1 in 20 germ cells and therefore 1 in 10 individuals of the next generation (if both parents were treated) to contain a newly induced mutant gene. To find the total detrimental effect of this on the population in the next generation we must therefore multiply $\frac{1}{10}$ by the arithmetic mean detriment produced by one newly arisen heterozygous mutant gene. Unfortunately, however, we cannot calculate this mean detriment from our value $\bar{p} = 40$. For $\bar{p}$ is not the reciprocal of the arithmetic mean detriment but of the harmonic mean detriment (in other words, it is the arithmetic mean of the reciprocals of the values for detriment of the individual mutant genes). There is no constant relation between arithmetic and harmonic means; a series of values with the same arithmetic mean may have very different harmonic means according to their pattern of frequency distribution. It hardly seems necessary to show our calculation of the probable maximum arithmetic mean detriment that may be assumed in the present case. However, it can be stated that unless the distribution of the detrimental values of heterozygous mutant genes in man is very different from that in *Drosophila*, with much greater grades of detriment the rule in man, the arithmetic mean value cannot be greater than $1/20$, i.e., 0.05. When this is multiplied by $1/10$ (representing the frequency of offspring having a newly induced mutant gene), we find a total induced detrimental effect of 0.005 (0.5%) among the immediate offspring.

That the mean heterozygous detriment is not above 0.05 is further indicated by consideration of Levit's studies, previously referred to (p. 132). When dealing with autosomal genes having the potentiality of giving conspicuous pathological effects in heterozygotes, he found that even these very seldom come to a level of expression where they can be readily recognized in more than a fifth of individuals carrying them. Since even when well expressed such genes are often expressed fairly late in life and so are not apt to lower the chance of perpetuation more than some 50%, their heterozygous detriment would usually average less than 0.10. Thus the far more numerous mutant genes that are relatively inconspicuous would have a much lower heterozygous detriment, and the mean value for all could hardly be above 0.05. This is further confirmed when we take into account along with this (1) the supposed autosomal recessives, since these are probably very weak dominants in the main, and (2) the sex-linked genes. As for the latter, a considerable majority of the genes known to be sex-linked had, as Levit showed, already been found to have some heterozygous expression. Yet this was usually too small and/or too infrequent in its detrimental effect to affect survival markedly, even though these genes were surely among the most conspicuous and therefore among the most extreme in detrimental effect.

We may therefore regard an over-all depression of viability of 0.5% as a probable maximum estimate for the effect, on the immediate offspring generation, of a 0.05 rise in mutation rate. This will of course be superimposed upon the at least 20% depression of viability that exists anyway, as a result of the equilibrium frequency of spontaneously arisen mutant genes. The two effects will however be combined in such a way as to cause the viability of the offspring of the treated parents to bear the ratio 99.5:100 (i.e. 199:200) to that of the offspring of non-treated parents. But all these values are expressed in terms of the detriment that would be produced under the primitive conditions to which the equilibrium of man had at some previous time become approximately adjusted. Under the modern conditions of disequilibration, occasioned by all the recently introduced ameliorative procedures, not only would there be a much less than 20% effect caused by the accumulated spontaneously arisen mutant genes, but a corresponding reduction below 0.5% in the effect of the newly induced mutant genes. Hence, under modern conditions, we may expect the viabilities to be much more alike than 199:200. It should be obvious that such a small amount of difference would be extremely hard to demonstrate convincingly even in an experiment with laboratory organisms, involving ideally controlled conditions and stupendous numbers.

Under the conditions of fluctuating environment, heredity and observation to which two human groups which were to be compared would necessarily be subject, it would be absurd to think that such a difference could be detected. And even if the difference were six times as great as this (as a result, let us suppose, of μ_t having been raised from 0.1 to 0.4 by a mean exposure of all the parents of the treated group to as much as 500 r) the ratio of genetic detrimental effects in the two groups would only be 97:100 without allowing for modern conditions, and this difference would be so small as to make a statistically valid demonstration of it, under existing conditions, very improbable. It is therefore highly unlikely that the observations being and to be made in the regions of Japan that were subjected to atomic bombing, where the dose of the survivors must have averaged a good deal less than the semi-lethal dose of 600 r, will show a statistically significant effect on the survival rate of the offspring, when all other possible sources of difference in the populations compared and in the conditions of observation are taken into account. The only chances of a demonstrable effect of such a nature would lie in the possibilities (1) that radiation raises the mutation rate much more in man than in *Drosophila*, contrary to some indications from work on mice, or (2) that the amount of effect of mutant genes in heterozygous condition is, on the whole, much greater in man than in *Drosophila*, and greater than present evidence in man himself indicates. Moreover, the same considerations as invalidate survival rate, measured in the immediate offspring, as the criterion of a rise in mutation rate, apply also to the measurement of other quantitatively expressed characters, such as height, strength, resistance to cold, morbidity, etc., for this purpose.

The principle should however be recognized that the more detrimental the effect of a mutant gene received from only one parent is, the more will a given rise in mutation rate raise its frequency among the immediate offspring, relative to the frequency of genes of the same kind that had already accumulated as a result of spontaneous mutation. This is because, other things being equal, the accumulation is inversely proportional to the degree of detriment. Therefore in cases in which highly detrimental genes can be recognized by some characteristic qualitative feature or syndrome that distinguishes their effects from those of the cumulative action of multiple genes of individually lesser effectiveness, and from those of environmental disturbances, these particular genes should furnish a much clearer index of a rise in mutation rate, provided the number of them that can be found is not too low from a statistical standpoint. To this group may also be added some genes not so markedly detrimental, such as achondroplasia or myasthenia gravis, of which the classification is so unmistakable and the penetrance so complete that newly arisen cases can be distinguished with certainty from those derived by inheritance, even where there is a possibility of illegitimacy.

The above stipulations mean that, for practical purposes, the best tests of mutation rate are probably furnished by those rare but individually conspicuous, fully penetrant, definitely classifiable, dominant anomalies, usually of strongly injurious nature, such as epiloia, which bulk so large in human genetic literature but form so small a part of the actually existing genetic differences in man. Genes of incomplete penetrance are ruled out here not only because they may be subject to variability in penetrance under different conditions but chiefly because (1) they are in effect less detrimental and therefore subject to a correspondingly higher degree of accumulation, and (2) cases of inheritance may be mistaken for new mutations. The same objections apply to "recessive" sex-linked genes such as hemophilia, which although strongly detrimental in the hemizygote have much less, if any, effect in the heterozygote. Their frequency even in the case of those which are fully lethal in the male must be nearly $3\mu_t$ and therefore would be much less diagnostic of a recent change in μ_t than that of dominant lethals would be. Unfortunately, when the prescribed conditions of highly detrimental action, full penetrance in the heterozygote and clear discrimination from possible environmental effects (such as those of prenatally contracted rubella) are all adhered to, the total frequency of origination of mutant genes known to be in this group is so low, in man as in *Drosophila*, as again to make exceedingly large numbers necessary for a significant result.

To illustrate this conclusion with a numerical example, let us suppose that as many as 25 mutant genes are already known to conform sufficiently to the conditions above given, that their average mutation rate is 1 in 50,000 gametes, and that on the average they persist through 1.5 manifestations. In an untreated population the frequency of all such mutant genes taken together would therefore be $25 \times 2 \times 1/50{,}000 \times 1.5$, or 15 in 10,000. Of these 15 there would on the average be 10 which represented newly arisen mutations, while 5 would be reappearances. Suppose now that, owing to the parents in a certain region having received an average of 200 r, the mutation rate had been doubled. There would in this region be 20 freshly arisen cases of mutation belonging to this category among 10,000 offspring, along with 5 reappearances, or 25 in all, to be compared with the 15 present among the 10,000 children of untreated parents. The numbers actually found would however be subject to a considerable statistical error (error of sampling). On account of this it turns out that, even if we could ignore the errors derived from all other sources, and if exactly the figures 25 and 15 were actually found, there would still be a fair chance (approximately 1 in 18) of our having found as great a difference as this in the absence of any real difference in mutation rate. If we could distinguish and discard the cases of inheritance, leaving just those of new mutation, we should have a somewhat more significant comparison: 10 versus 20. On the other hand, we might very well have happened to find, for example, the numbers 13 and 18 new mutations in our samples of 10,000 offspring of the exposed and unexposed groups, even though the mutation rate had in fact been doubled. These numbers, however, could have resulted about equally readily if the mutation rates had been the same. Thus in that case our observations would have given us no basis to conclude that there had been any effect at all of the radiation on the mutation rate. It seems very unlikely, however, that the number of different kinds of distinctive dominant abnormalities, of a type that would at present be recognized, would be nearly as high as 25.

We see then that although there is some possibility that the studies in Japan may obtain evidence of the induction of mutations, it is certainly premature to say, as some persons have done, that they will afford a definitive test of the genetic effectiveness of radiation in man. Assertions have in fact been made that if positive results are *not* found there, this will have a salutary influence in quieting public fears concerning the genetic dangers of radiation. It should therefore be reiterated that existing knowledge is not only enough now to make it more likely that no definitely positive effects will be found than that they will, but also enough to make it quite sure that such failure to obtain positive results would not give valid support for the view, thus far based only on wishful thinking, that the amount of effect is insignificant.

We saw in the preceding section how important in the long run an amount of mutational increase may be which is too imperceptible to be noticed in one generation, provided this increase in rate is long continued. But even an increase in mutation rate which is confined to but one generation is in the long run important enough, in human terms. We cannot notice its effects because of the variations caused by other, fluctuating factors, and because its effects are spread out so thinly, that is, over so many generations (over 40, on the average, if $\bar{p}$ is 40). If however these effects could be collected together we would not fail to be impressed by them. Thus, in a population of 100,000,000, a rise of mutation rate of only 0.025, confined to just one generation, would in the course of centuries result in 5,000,000 genetically caused extinctions, and in a vastly greater number of individuals who were detrimentally affected to a slight extent.

18. On the likelihood of increase in the human mutation rate.

It might be imagined however that the average person would be very unlikely to receive a dose of radiation great enough to raise the mutation rate by 0.025. But it takes a total dose of only about 50 r, when applied to the immature germ cells of *Drosophila*, to cause this much rise, and only 25 r when applied to mature germ cells. Moreover, the data from mice, although entirely too scanty, do indicate so far as they go that the induced mutation rate in mammals is of the same order of magnitude as in *Drosophila*.

Now 50 r is an amount of radiation that a person's gonads are not at all unlikely to receive under modern conditions. And the use of radiation is increasing in so many ways that, within a few decades, people whose gonads have not been exposed to this much total radiation, in the entire period from their conception to the time they reproduce, may be comparatively rare. A single fluoroscopic "screening" has been estimated to deliver to the skin about 75 r, on the average (Martin, 1947), and although but a fraction of this reaches the gonads it would not take very many such examinations to deliver 50 r to them. Again, an increasing number of women are having their ovaries deliberately treated with 300 r for the purpose of rupturing refractory Graafian follicles, i.e. to induce ovulation (see for instance Haman, 1947), and the practice of having the testes treated with 500 r for the purpose of delaying the possibility of conception for several years is said to be increasing in popularity among men.

At the same time as the uses of penetrating radiation and of radioisotopes in medicine, both for therapy and for diagnosis, are increasing, commercial practice is taking up these agents for sales purposes, as in shoe stores, and there are ever increasing industrial applications, as in testing for internal faults in metallic structures, in the removal of electrostatic charge, and in various applications of electronics. When to all this we add the probability that the use of atomic energy and of its by-products is only at the beginning of a great process of expansion it will readily be realized that 50 r is by no means a fantastic estimate for the average dose to which an individual's germ cells will be likely to be exposed in each generation anew, unless measures are employed which have as their express object the prevention of this much accumulated exposure.

As yet, there is much resistance to such measures when they are proposed. Indeed, even the "permissible level" of 0.3 r per week which has recently become commonly recognized (but not so commonly followed), and which represents a considerably more cautious standard than the long-accepted "tolerance dose" of 0.1 r per day that preceded it, would allow 15 r a year. Hence it would allow delivery of 50 r in the course of only three and a third years. It should therefore be evident that present peacetime trends, unless subjected to more effective checks than would now be favored by most of those dealing with radiation, may lead to a sizeable and long continued increase in the mutation rate. What might happen genetically if, as a result of atomic warfare, appreciable quantities of long-term radioisotopes became distributed over large areas, is another matter which requires most serious consideration, since responsible physicists conversant with the possibilities in this field regard this danger as a very real one. We are not prepared to deal with it here, however, in the absence of estimates of how much radiation might be received in this way.

It would also take us too far afield to consider here the various influences other than radiation which are known to affect mutation frequency, such as mutagenic chemicals, age and sex. The interpretation of their manner of action depends in part on a question raised by the present writer (1928*b*), as to whether most mutations are mistakes in gene reproduction or permanent changes in the completed gene. Evidence has accrued indicating that both kinds of changes occur but that in most types of cells the former are perhaps the more usual kind. Whatever the answer to this and related questions of mutational mechanisms may be, they will have a bearing on our judgments concerning the genetic effect on populations of various features of their mode of life. Some of these influences—for instance, the age of the male when he reproduces, according to a study of Haldane's (1947*b*)—may increase the mutation rate even more markedly than radiation is likely to do. Moreover, since, as previously explained, the human mutation rate is probably not far from its critical level, even mild influences may turn out to be of more significance than has been suspected, in relation to the mutational load of mankind. Therefore, in view of the great changes in mode of life which civilization is bringing about, including exposure to unusual chemicals, alteration in average age of reproduction, etc., it is of ultimately practical importance to obtain more knowledge of the effects of these conditions on the mutation process.

19. Motivations and criteria for genetically acceptable practices.

Despite our insistence in the foregoing that indefinitely prolonged continuance of the present pattern of reproductive behavior along with a continuance of modern medical practices and of the now prevailing attitude toward radiation, would eventually lead to grave genetic consequences if not to complete disaster for mankind, it is not our intention to leave the impression that there is in this situation a cause for acute present alarm. For, as we have also pointed out repeatedly above, the process is a very long term one, the great genetic changes being, in terms of human affairs, very slow. Fortunately men's mental attitudes, especially under modern conditions, are subject to far more rapid changes on a grand scale than their genes are. Thus it would seem absurd to suppose that, if civilization succeeds in surviving the present world crisis in a progressive form, the present disregard of biological fundamentals will persist indefinitely.

At the same time, we must recognize that such far reaching changes in attitudes and practices as are called for in this field will not develop of themselves. It is the responsibility of those who already have knowledge of the genetic facts to be prime movers in driving home an adequate realization of them among both the lay and medical public, and among all groups concerned with social matters, until appropriate changes are adopted in their daily practices and precepts.

We must be prepared for a long uphill struggle, at best, before this can be accomplished. This is because, for one thing, the penalties for wrong behavior in regard to these matters are so completely hidden from direct observation and are so remote in time, while even the proof of their existence requires a process of ratiocination that the average man is not prepared to follow readily, nor to be impressed by. Rather will he be inclined to give priority to his immediate concerns, the interests of which will often (at least under existing mores) run counter to those of the seemingly immaterial abstractions conjured up by the geneticist. Supporting him in this course will be powerful groups of persons having vested material interests in present techniques and practices, as well as other powerful groups, whose interests lie in the preservation of antiquated ideologies in general.

Only after the opposition of these last, more especially, has become sufficiently weakened to allow the conception of evolution, including that of its genetic mechanism, to become as much a cornerstone of elementary education as the rotundity of the earth, and after the processes and consequences of genetic change throughout the ages have been vividly visualized and dramatized for people in general from their early years on through their later development, can we expect the arguments, calculations and recommendations of geneticists to take on sufficiently concrete meaning for the average man, the medical man, and the man in public life, so as to influence them adequately in their conduct of practical matters. To work for this modernization of educational policy and methods, with a view to reshaping the average man's view of his place in nature, is therefore one of the first duties of those who appreciate the significance of genetics in human affairs.

But even if we were quite convinced that humanity would not be content to continue indefinitely along the road to an actual genetic denouement, we should not for that reason feel justified in regarding the matter of mutational load as one of little consequence. Just because a practice will not result in the wiping out of the human race is no reason why we should go to the other extreme, of considering it innocuous or negligible, as some would have us do in the case of radiation as soon as they find that an atomic bomb will not result in a population of monsters. A practice should be regarded as salutary or pernicious according to the amount of its total benefit weighed against the amount of its total detrimental effect. In the case of practices affecting heredity and reproduction, we must extrapolate and find the probable total long-term advantage or harm. For a good or evil that we do is not made less by its being far removed from us in distance or time. Now the accumulated long-term benefit or harm caused by a one-generation treatment happens to be equal to the amount of change that would affect each single generation if the same treatment were to be indefinitely continued. Thus, if an average of 100 r were applied to the germ cells of the whole population for an indefinitely long period and finally lowered the equilibrium fitness by 10%, then the application of 100 r to just one generation would have a total genetic effect equivalent to the lowering of the average fitness of exactly one whole generation by 10% (implying with this an increment of 10% in its genetic deaths). Actually, however, these 10% of deaths and these forty ($\pm$) times as numerous slight shortcomings would be diluted by being spread out over scores of generations. If then we knew this relationship we should have to put the further question: would the benefits of applying just these particular practices, rather than such substitutes or modifications of them as would not have this genetic effect, be worth so large a price?

A similar question would have to be raised regarding the effects of improvements in living conditions and in medicine on selection. And here of course the modification of practice to be considered would surely consist, not at all in the withholding of the benefits of modern knowledge and techniques for the improvement of the individual, but, as pointed out on pages 150–151, in his suitable education and advisement, in such wise as to result in the genetically more afflicted individuals, of their own volition, deciding to transmit, on the whole, fewer of their genes, by an amount at least sufficient to maintain the equilibrium.

Now just as we judge of the total effect on the population of a reproductive practice that is carried on for a limited time by taking the corresponding fraction of the equilibrium effect which it would have if it were indefinitely continued, so too we can best judge how much effect it would have when applied to only a limited section of the population, or even to just one individual, by extrapolating backwards, so to speak, from the equilibrium effect on the whole population. This gives us a criterion for justifying or condemning the given practice even in the most limited sphere of its application. For example, if 100 r, applied as an average to a whole population, indefinitely, causes a 10% lowering of average fitness and a corresponding 10% increment of genetic deaths, then this 100 r applied to the germ cells of just one individual who will later reproduce by an average amount will cause, again on the average, a total lowering of fitness of his descendants equal to the lowering of fitness of one descendant by 10%, and will, correspondingly, give a 10% risk of one genetic extinction, occurring at some unknown point in his line of succession. Nevertheless, if we have thereby raised the level of life of the exposed individual himself to such a degree that the effect, when averaged out over his own lifetime, would amount to more than 10%, then we were in fact justified—provided we could not have attained this benefit by means that were safer for his descendants. And the same kind of considerations must be the guide in decisions concerning whether or not a given individual should undertake reproduction, when he is known to have certain genetic shortcomings.

20. The mutational load in relation to mental traits.

It should be obvious that the same general principles apply to the inheritance of intellectual capacities and emotional proclivities as to the so-called physical traits. It is true that mental traits are in general much more modifiable, in their phenotypic expression, by the action of environment, including social environment of all kinds, such as community and family traditions, education and individual experiences. Yet, so far as the genetic basis of mental traits is concerned, the processes of mutation and selection and the laws concerning the rise and fall of gene frequencies, equilibria, etc., apply in the same manner. Moreover, it is likely that, in man especially, the number and complications of genes having to do with mental traits is exceedingly great, so as to result in a comparatively high mutation frequency, one requiring a considerable compensatory selection for the mere maintenance of equilibrium.

In the case of mental traits even more than of those having to do with general health and vigor, there is reason to conclude that selection has greatly relaxed under modern conditions. In fact there is even evidence of a reversed selection in some important respects—a process which could much sooner lead to results that were marked enough to be detectable in the descendants. But whether or not there is a significant amount of reversed selection, it must be recognized that, as in the case of general health, the mutation rate cannot be raised, nor can selection be relaxed, without the equilibrium being altered in the direction of deterioration. And while we can for a time compensate for such a decline, as we are now doing, by better education and general environment, including the more efficient utilization of ability, still this would in the long run be a losing battle unless equilibrium were again allowed to be attained, and at a level sufficiently rigorous to allow the maintenance of these expert, easily mishandled euthenic operations.

Most of us will agree that, for man, it is the world of mental life which counts by far the most, the rest being pretty much subsidiary. It is therefore evident that, if we ever come to weigh the relative values of different genotypes for reproduction, the genes concerned with mentality, could we estimate them at all, would on the whole have the higher priority. How inadequate even most scientists must feel, in this so-called scientific age, on reading of the new conceptions of Einstein! Greater intellectual capacity, and along with it kindlier natural feelings, are surely the greatest biological needs of all humanity. And so, although we must assiduously seek out the knowledge of the principles that make the genetic basis of our physical health, and strength what they are, and of means to improve them, we must not forget that the transmission of a few more genes for slight physical infirmities here and there are usually far more than compensated for when they happen to make possible some considerable betterment of the genetic basis of these mental characteristics. We must remember too that in such cases, thanks to gene recombination processes, the genes will become reshuffled in subsequent generations, and we will thereby soon be relieved of the need for continuing the opportunistic compromise whereby the more precious elements were saved at the price of some physical defects.

It follows from these considerations that, for mankind, we cannot take the old par values of nature, in respect to each trait, as the present or future optimum, but should, if we can, readjust the direction of aim of the genetic processes. This revaluation is not merely of mankind's choice. It is forced upon him if, merely to compensate for the interference which modern conditions "of themselves" work in the age-old equilibrium levels, he finally realizes the *necessity* of exercising some guidance over his reproduction.

21. Survey of conclusions regarding the mutational load as affected by dominance.

We have seen that the findings on the genetics of lower forms, particularly *Drosophila*, taken in connection with the facts already at hand from human genetics—between which fields there is remarkable agreement—have shown the total mutation rate to be much higher than usually imagined. Moreover, it is this total rate which determines the mutational load—counting even the smallest mutations as equal to the largest in their final detrimental action on the population.

Secondly, the accumulated evidence concerning dominance, recently very much strengthened, has made it highly probable that the great majority of mutant genes exert their main detrimental action on the population in heterozygous condition, as weak but "effective" dominants, and that they are mainly eliminated through this heterozygous action. Acting as an effective dominant, each such gene has nearly twice as much total detrimental effect on the population as a complete recessive would have. This dominance however causes each mutant gene to persist in the population for a much shorter time, on the average, than had previously been reckoned, although this time is still to be counted in hundreds or thousands of years, according to the case.

As a result of the effective dominance, the effects of changes in mutation rate, such as might be produced by mutagenic agents, become manifested much earlier and more directly than had been reckoned when most mutations were dealt with in calculations as though they were complete recessives, even though the effects still accrue too slowly to be directly observable. Equilibria too are thereby approached more rapidly than reckoned before. Moreover, the results in general are much less influenced by variations in the system of breeding than they were thought to be.

As the dominance must usually be slight enough to allow a considerable number of reappearances in heterozygous condition, probably averaging tens of "reincarnations" even for many genes which when homozygous would be highly detrimental, it can be reckoned that practically every individual suffers from the disadvantage of possessing several or many slightly detrimental genes that attain some degree of expression and act to hamper him. Their number then is greater and their individual effect is smaller than if they had acted mainly as recessives. As a rule the resulting "abnormalities" will be minor inadequacies, of a nature similar to the effects of adverse environmental conditions, more or less cumulative with the latter and therefore, like them, with symptoms that are usually more or less remediable; in fact, the same regimens or treatments should often work against them as are used to counteract the purely environmental effects. Nevertheless, they are numerous enough to be collectively important, in the great majority of individuals, and, untreated, they must lead to the "genetic death," or extinction, of a sizeable proportion—at least some 20%, to be conservative, of the population. On the other hand, if these weaknesses are mitigated or "cured" and in consequence proceed to perpetuate themselves to a greater degree than before, they must eventually, after very many generations, result in a new equilibrium, in which the population harbors and is being treated for correspondingly more of them than before, and in which there is again, despite all these treatments, just as large a proportion meeting genetic extinction as there was originally. At the same time, the amount of genetically caused suffering short of extinction will also have become comparable with what it had been originally.

The existence of this small degree of dominance implies that selection, whether down or up, has been, despite its slowness, much faster working and more direct in man than it has usually been assumed to be. The phenotype thus becomes a better guide to the genotype, and detrimental genes can be eliminated more rapidly and more nearly to completion than on our previous view. Moreover, in the presence of positive selection too, change will be quicker and surer. In this connection it is especially to be noted that, on modern conceptions of dominance, it must have been changes of the more detrimental types which have come to have the more complete recessiveness. For in the case of detrimental mutations of lesser degree, unless they are merely lesser editions of other, more extremely detrimental mutant genes, there would have been correspondingly less selection for dominance of the normal type. Still more would this be the case, on the whole, with mutations of indifferent survival value, and with those rare changes which are actually advantageous—that is, they would tend to have even more dominance in relation to the "normal" gene from which they originated.

In view of this dominance, it is not so strange that children often resemble their parents so markedly, and present such an apparent blend of the individual peculiarities of the two parents, even in those cases in which the children are derived from crosses between widely separated groups, who would have relatively few recessive mutant genes in common. Nor is it strange that the correlation between brothers and sisters is not so much greater than between parent and child. Again, it becomes more understandable why even the brother-sister crosses of Pharoahs, Incas, and some other peoples should have been as successful as they were, for there would be fewer hidden recessives. And it fits in with the findings of Halperin, that although the rare, extreme grades of mental deficiency do arise from parents who appear to have a nearly (although apparently not quite) normal distribution of intelligence, the much commoner, milder grades have parents who are on the whole distinctly below normal themselves. We do nevertheless contain many hidden mines, recessive lethals and strong detrimentals, capable of destroying our offspring, but they are neither as many nor as hidden as we had thought.

The same considerations make more intelligible to us the results indicating that in the domestic and laboratory animals, which surely agree with us substantially in these respects, selection for, say, larger size or racing ability or egg production, even when not combined with close inbreeding, has enabled us rather rapidly to advance towards our objectives. Dealing with numerous partially dominant genes, many of them with individually slight effects, we have not needed to know the exact genetic formulas, but could make much progress by simpler, more empirical and direct means, much as nature does but faster.

Of course, in man as elsewhere, there will sometimes be a gene whose homozygous effect is excessive or even qualitatively detrimental, despite the fact that it is actually advantageous as a heterozygote. But, even so, this price is sometimes worth paying, when it gives us quickly what is much needed, and thus helps to tide the stock over until the gene in question can be "buffered," or until a more reliable one can be substituted.

There is a world of work to be done in the study of our mutations: of the causes which condition their origination, their comparative expressions as homozygotes and heterozygotes and in varied combinations with one another and with environmental conditions, their present total frequencies, the distribution of frequencies among those with different grades and types of manifestation, and the impact of conditions upon the selection of them. Moreover, the intensive studies of individual mutant genes must be pushed, for this is a requirement for learning more about the mutant genes in general and about the mechanisms of development and physiology. But it must be remembered that there are thousands, or even, counting multiple alleles, hundreds of thousands, of different mutant genes, each one with its own complications. And yet, before the ideal exact knowledge of these genes considered individually and intensively is attained, we can already see in a general way how, through their more or less cumulative action, mainly as partial dominants, the child comes to resemble its parents and the idiosyncracies noted by the good old family physician and allowed for in his treatments do tend strongly to run in families.

Thus, the ailments and infirmities caused by mutations, although they are perhaps not so often a "direct cause of disease," or at least of the once rampant infectious diseases that are now rapidly being overcome, are nevertheless of vital importance to all of us. None of us can cast stones, for we are all fellow mutants together. In this connection, however, we may be glad that the harmful mutations have an appreciable degree of dominance, for this will make it more feasible to follow them up and to deal with them. At the same time, the benefits potential in the far rarer advantageous mutations must continue to constitute our ultimate biological hope. Thus it is an even more fortunate circumstance that (at least if our genetic theory is correct) the advantageous mutations have a higher average degree of dominance than the detrimental ones.

GENERAL RÉSUMÉ

1. It is shown that, contrary to the view alleged to have been prevailing in medical circles, according to which mutation is virtually negligible as a cause of disease in man, it must in human populations that live in a state of approximate genetic equilibrium be the differential cause of the death or failure to reproduce of between one-fifth and two-thirds of the persons who escape being killed before reproduction, or being prevented from reproducing, by other, purely extrinsic causes.

2. The above conclusion is arrived at by the use of Danforth's (1921) fundamental theorem of genetic equilibrium. According to this, the frequency with which a given mutant characteristic is present in a population is equal to the frequency with which it arises by mutation, multiplied by the average number of generations during which a gene for the given characteristic has been able to manifest itself before being eliminated by reason of the disability it confers. Examples and extensions of the theorem are discussed. In applying it for the purpose of deriving the conclusion stated in the preceding paragraph, it was necessary to have estimates of the total mutation rate and of the usual amount of dominance.

3. On the basis of existing data in man, supported by evidence from *Drosophila*, the total human mutation rate is judged to be probably not less than one newly arisen mutant gene in 10 germ cells, on the average, and not more than one in 2 germ cells.

4. Evidence is presented in support of the finding of Levit (1935, 1936) that the great majority of mutant genes in man have some degree of dominance. It

is shown that, both in *Drosophila* and in man, although most mutant genes are recessive in the sense of producing less than half as much aberration when heterozygous as when homozygous, nevertheless they are "effectively dominant," in the sense that most of their total damaging effect on the population is exerted through their action while in heterozygous condition.

5. The probable distribution of mutant genes with regard to the amount of detrimental effect which they produce when homozygous and when heterozygous is considered. It is estimated that, although "effectively dominant," the mutant genes of a given locus usually produce, in any single individual, but a very small effect when heterozygous, but accumulate until they reach a reciprocally high frequency in the population, and so do as much total damage as if they were completely lethal. It is calculated that the average individual is probably heterozygous for at least 8 genes, and possibly for scores, each of which produces a significant but usually slight detrimental effect on him. (The number thus arrived at would vary greatly according to the exact grade of detriment at which the line was drawn between genes designated as significantly detrimental and those designated as practically indifferent for survival, in view of the high degree of accumulation of genes of the borderline kinds.) All the detrimental genes together tend to give each individual his own characteristic, more or less familial pattern of weaknesses, most of which however are not to be distinguished sharply from disabilities of environmental origin and which are intimately combined with the latter.

6. The number of mutant genes in different individuals forms approximately a Poisson series. Those individuals who undergo genetic elimination, constituting some 20% or more of populations living in a state of genetic equilibrium, do not on the average have much more than one gene in excess of the survivors and are therefore not, as a group, markedly inferior to them. In correspondence with this, the great majority of individuals suffer from a genetically occasioned depression of viability approximately great enough to result in a risk of extinction that is equal to the frequency of individuals who do become genetically eliminated in each generation.

7. The above estimates of the frequency of extinction due to genetic causes and of the amount of depression of viability of the average individual apply only to a population living under the same conditions as those which existed while approximately the present gene frequency was being established (i.e. under the conditions for which it represents an equilibrium). The improvements in living conditions, medicine, etc. under our modern civilization must result in a saving for reproduction, at present, of a large proportion of those who under the earlier conditions would have been genetically proscribed, and in a corresponding mitigation of the effects of the genetic disabilities of the great majority of the population.

8. If, as at present happens, the individuals saved for reproduction by these

procedures actually do reproduce, the mutant gene frequency will gradually rise in the direction of a new equilibrium level (probably not half attained a thousand years from now even if conditions remained constant in the interim). At the new level, despite the ameliorative measures, as large a proportion would again suffer genetic elimination as under primitive conditions, while those not eliminated would again be as much afflicted as originally. A much greater proportion of their time and effort than at present would then be expended in the attempt to counteract their accumulated internal disabilities (which would amount to lethality for the great majority of them if they again had to live under primitive conditions), rather than difficulties of external origin. It is unrealistic to suppose that technique could continue to advance indefinitely to such an extent as to avoid this denouement.

9. It is shown that the only means by which the effects of the genetic load can be lightened permanently and securely is by the coupling of ameliorative techniques, such as medicine, with a rationally directed guidance of reproduc tion. In other words, the latter procedure is a necessary complement to medicine, and to the other practices of civilization, if they are not to defeat their own purposes, and it is in the end equally as important for our health and well-being as all of them together. Under this procedure, if it is to be successful in attaining its objectives by means consistent with its aims, the equilibrium quota of detrimental genes must become eliminated as a result of voluntary decisions and not as a result of failure in a struggle for existence.

10. It is also shown, with the aid of a numerical illustration, that highly developed knowledge of human genetics would, theoretically at least, make possible the elimination of the necessary quota of mutant genes by means of the abstention from reproduction of a much smaller proportion of individuals than that proportion (equal to nearly twice the mutation rate) whose elimination is required for equilibrium under ordinary natural selection. This would be made possible by the systematic choosing, for such abstention, of individuals having an especially high excess of mutant genes, beyond the average number.

11. A long-term increase in the mutation rate, if of moderate degree, would eventually result in a proportionate increase in the genetic load (e.g., a doubled rate would double the load), if the load were expressed in terms of either the proportion of the population suffering genetic elimination or the amount of disability suffered by the average individual.

12. If the long-term increase were of more than moderate degree, however, the mutation rate might have exceeded the "critical value", beyond which equilibrium was impossible and extinction of the population was (if the conditions continued) inevitable. For the usual mutation rate of man must be not far below the level which would have been critical under primitive conditions of reproduction. But in the presence of the low rate of reproduction prevailing among most of the technically advanced peoples, the present mutation rate

must be very nearly at or is perhaps even beyond the value which is critical in this situation. Under these circumstances even a moderate increase in mutation rate, such as one of 25%, might be more than could be tolerated indefinitely.

13. The use of ionizing radiation and of radioactive materials is increasing and promises to continue increasing to such an extent, both in medical treatment and diagnosis, and in commerce and industry, even without considering military affairs in this connection, that unless more caution is exercised than at present the majority of the population may in each successive generation have its gonads exposed to enough radiation to raise the mutation rate by a significant amount, such as 25% or 50%.

14. How much a given exposure increases the mutation rate is a matter that cannot readily be determined by observations on human or other indiscriminately breeding populations. Even a quadrupling of the mutation rate, occurring throughout a whole population for just one or a few generations, would probably affect the viability of the descendants in too scattered a manner (see paragraph below) for these effects to be distinguished from those of uncontrolled circumstances. Moreover, vast numbers would be necessary for the finding of statistically significant differences in the frequency of clear-cut mutational abnormalities.

15. Yet despite the fact that the evidence of a short-term rise in mutation rate is so hidden, the total amount of damage caused to all later generations by even a moderate rise, confined to one parental generation, would if gathered together be seen to be enormous. Thus only a 25% rise in mutation rate for one generation would, in a population of 100,000,000 per generation whose usual spontaneous rate was only 1 mutant gene in 10 germ cells, cause the eventual "genetic death" of 5,000,000 individuals, scattered throughout scores of generations. It would probably cause, in addition, hundreds of millions to be slightly more afflicted than they would otherwise have been, i.e. to have their viability lowered by an average of some 2 or 3%. These effects are hidden only because distributed over so many generations and because so intermingled with those of other factors. Moreover, once the mutations have been produced, they will take their eventual toll despite all counteracting measures that may hereafter be instituted, short of a consciously directed selection.

16. The total effect eventually exerted, over the course of an unlimited number of generations, by a given one-generation rise in mutation rate, although hidden from view, is quantitatively the same as the effect which would be observable in any single generation if an increased mutation rate of the same magnitude were indefinitely continued and equilibrium for it had been reached. Similarly, the total average magnitude or risk of effect in subsequent generations when only a small part of the population or even one individual has had his mutation rate raised is proportional to the above mentioned effect

which would be observable in one generation in an entire population that had reached equilibrium for the given rate, and may be expressed in terms of the probable number of descendants meeting genetic extinction or of the corresponding total amount of genetically occasioned affliction. These values for a given number of r units applied to human material remain to be determined, however, and until they are we cannot well judge of the value or disadvantage of procedures which, in helping the immediate generation, cause an unknown amount of damage to subsequent ones.

17. Attention is called to social obstacles which tend to prevent the medical and lay public, educators, and administrators from recognizing the above principles and from taking steps to modify current attitudes and practices in accordance with them. In this connection fundamental educational reforms—the institution of which, unfortunately, is subject to the same hindrances—are needed.

18. It is pointed out that mental traits are subject to the same principles regarding mutational load, selection, equilibrium, etc., as have been reviewed above for physical traits but that, being more important for man, they should be given first priority.

19. A number of important changes in our point of view regarding genetic processes in man are called for by consideration of the fact that most mutant genes have a certain degree of dominance, usually enough to be "effective", and probably greater in the case of the less detrimental mutant genes than of the more detrimental ones. It is seen, for example, that equilibria, though still very slow of attainment, are not nearly as long delayed as on the older view; that selection, both negative and positive, is more effective and rapid in its action than had been thought; and that the amount of inbreeding practiced becomes a matter of somewhat lesser consequence. In general, previous discussions and calculations will require major revision, in order to be brought into line with this altered genetic outlook concerning dominance.

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